Activity in somatosensory cortices during stroke recovery

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Abstract

The aim of the thesis was to examine how activity in somatosensory cortex changes during stroke recovery by analysing previously-recorded magnetoencephalographic (MEG) responses to tactile pneumatic stimulation and passive movement of the right and left index fingers. The measurements were made for 23 stroke patients with upper limb paresis at acute phase, one month and 12 months after stroke. To our knowledge, this is the first follow-up study to research somatosensory evoked responses to passive movement in several stroke patients.

The activity in somatosensory cortices evoked by both tactile and passive stimuli increased significantly from the acute phase to 12 months post-stroke in both affected and unaffected hemispheres. In addition, the activity was stronger in patients than in healthy control subjects at 12 months after the stroke symptoms in both hemispheres. In healthy subjects, the SEF-response amplitudes are approximately equal in two hemispheres whereas the patients had weaker responses to tactile stimuli in the affected (AH) than the unaffected hemisphere (UH) at one month after the stroke. In contrast to tactile stimuli, no significant differences between the contralateral affected and unaffected hemispheres in the passive movement were observed. However, both tactile and passive stimuli elicited enhanced activity in the ipsilateral unaffected hemisphere with respect to the impaired hand stimulation during the whole follow-up year.

In conclusion, the results confirmed that a stroke changes both proprioceptive and tactile information processing and a unilateral stroke affects both hemispheres. Moreover, the results indicate that the activity changes during one-year follow-up, which refers that neural changes occur within first three months but can continue significantly up to 12 months. Enhanced activity in the healthy hemisphere may be associated with incomplete functional recovery.

Keywords Somatosensory evoked fields, primary somatosensory cortex, secondary somatosensory cortex, tactile stimulus, passive movement, stroke, follow-up, MEG, MNE Python

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Tiivistelmä

Diplomityön tarkoituksena oli tutkia, miten somatosensoriset herätevasteet muuttuvat aivohalvauksen aikana analysoimalla aiemmin magnetoencefalografilla (MEG) mitattuja etusormen tuntoärsykkeen ja passiivisen liikkeen aiheuttamia herätevasteita somatosensorisella aivokuorella. Mittaukset oli tehty 23 aivohalvauspotilaalle, joilla oli infarktin aiheuttama yläraajan halvaus 1-7 päivää, kuukausi sekä 12 kuukautta aivoinfarktin jälkeen. Tietämyksemme mukaan tämä on ensimmäinen seuranta-tutkimus, jossa tutkitaan ja vertaillaan passiiviliikkeen aiheuttamia somatosensorisia herätevasteita usealla aivohalvauspotilaalla.

Sekä terveen että halvaantuneen käden stimulaatioiden aiheuttamat herätevasteet kasvoivat toipumisen aikana molemmilla aivopuoliskoilla ja olivat voimakkaampia potilailla kuin kontrolleilla vuoden jälkeen aivoinfarktista. Normaalisti terveillä ihmisillä kahden eri aivopuoliskon vasteet ovat suunnilleen yhtä voimakkaat, kun taas potilailla etusormen tuntoärsykkeen aiheuttamat vaurioituneen aivopuoliskon vasteet olivat tervettä heikommat. Toisin kuin tuntoärsyke, passiivi liike ei aiheuttanut merkittäviä eroja terveen ja sairaan aivopuoliskon aktivaatioissa. Kuitenkin sekä tuntoärsykkeen että passiivisen liikkeen aiheuttamat ipsilateraaliset vasteet sairasta kättä stimuloitaessa olivat poikkeavan voimakkaat terveellä aivopuoliskolla koko seuranta vuoden ajan.

Tutkimuksen tulokset osoittavat, että aivohalvaus muuttaa sekä proprioseptiivisen että tunto informaation käsittelyä ja muutoksia havaitaan terveessä ja sairaassa aivopuoliskossa. Lisäksi tulokset osoittavat, että stimulusten aiheuttamat herätevasteet muuttuvat yhden vuoden seurannan aikana, mikä viittaa siihen, että aivojen hermosoluissa ja aivokuorella tapahtuu muutoksia kolmen ensimmäisen kuukauden aikana, mutta ne voivat jatkua merkittävästi jopa 12 kuukauden ajan. Poikkeavan voimakas aktiiviisuus terveellä aivopuoliskolla voi vaikuttaa negatiivisesti toiminnalisten kykyjen palautumiseen.

Avainsanat Herätevaste, tuntoaivokuori, aivoinfarkti, tuntoärsyke, passiiviliike, seurantatutkimus, MEG, MNE Python

Preface

I want to thank Docent/Adjunct Prof. Nina Forss and Prof. Lauri Parkkonen for giving me the opportunity to write the thesis on such an interesting topic. I would also like to thank my family for all the support they gave me and took care of my small children during my studies. In addition, I am very grateful for my study colleague and friend Gustaf Lönn who gave me important advice and helped me with problems that I faced during the research process.

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Contents

Abstract 3

Abstract (in Finnish) 4

Preface 5

Contents 6

Abbreviations 8

1 Introduction 9
1.1 Aims of the study . . . 11

2 Background 12
2.1 Somatosensory system and somatosensory cortex . . . 12
2.1.1 Somatosensory pathways . . . 12
2.1.2 Primary somatosensory cortex (SI) . . . 13
2.1.3 Secondary somatosensory cortex (SII) . . . 14
2.1.4 Posterior parietal cortex (PPC) . . . 15
2.2 Magnetoencephalography . . . 15
2.2.1 MEG instrumentation . . . 15
2.2.2 MEG vs. EEG . . . 17
2.2.3 Neural basis . . . 17
2.3 Somatosensory evoked responses . . . 20
2.3.1 Electrical stimulation . . . 21
2.3.2 Tactile stimulation . . . 22
2.3.3 Proprioceptive stimulation . . . 23
2.4 Stroke . . . 24
2.4.1 Types of stroke . . . 24
2.4.2 Brain plasticity . . . 25
2.4.3 Recovery and reorganization . . . 25
2.4.4 Somatosensory evoked fields in Stroke . . . 26

3 Methods 28
3.1 Patients . . . 28
3.2 MEG recordings . . . 28
3.3 Tactile stimulation . . . 28
3.4 Passive movement . . . 29
3.5 Data analysis . . . 30
3.5.1 MNE software package . . . 30
3.5.2 Steps for data analysis . . . 31
3.5.3 Preprosessing . . . 31
3.5.4 Epoching and averaging . . . 31
3.5.5 Channel selection . . . 32

3.5.6 Grand averaging . . . 33
3.5.7 Peak amplitudes . . . 33
3.5.8 Response energy calculation . . . 34
3.6 Statistical analysis . . . 34

4 Results **35**
4.1 Tactile responses . . . 35
4.1.1 Grand averages . . . 35
4.1.2 Response amplitudes and latencies . . . 39
4.1.3 Response energy . . . 41
4.2 Passive movement . . . 43
4.2.1 Grand averages . . . 43
4.2.2 Response amplitudes and latencies . . . 47
4.2.3 Response energy . . . 49

5 Discussion **51**

6 Conclusions **56**

References **57**

A *p*-values of the statistical analysis (tactile stimulus) **64**

B *p*-values of the statistical analysis (passive movement) **65**

Abbreviations

AH	Affected hemisphere
AP	Action potential
CNS	Central nervous system
ECD	Equivalent current dipole
EEG	Electroencephalography
EOG	Electrooculography
fMRI	Functional magnetic resonance imaging
ISI	Interstimulus interval
MEG	Magnetoencephalography
MNE	Minimum-norm estimation
PPC	Posterior parietal cortex
PSP	Postsynaptic potential
SD	Standard deviation
SEF	Somatosensory evoked field
SEM	Standard error of mean
SEP	Somatosensory evoked potential
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
SNR	Signal-to-noise ratio
SSS	Signal space separation method
SQUID	Superconducting quantum interference device
tSSS	Temporally extended signal space separation method
UH	Unaffected hemisphere
VPI	ventro-postero-inferior nucleus

1 Introduction

Stroke is one of the major causes of disability in adults. About 75% of stroke patients have a motor deficit in the upper limb initially after the stroke (Feys et al., 2000). Impaired upper limb functioning hampers everyday living as well as ability to work and is therefore a major challenge in rehabilitation after stroke (Lindberg et al., 2004). The mechanisms of brain recovery after stroke remain incompletely understood. Stroke recovery is based on reorganization of the central nervous system, but the temporal development of the recovery is still not very well known (Roiha et al., 2011). It is known that most recovery occurs within 6 months post-stroke (Jørgensen, 1996) but it may continue for up to one year (Bonita and Beaglehole, 1989). If it was possible to predict early the level of recovery a patient might reach, appropriate medication and rehabilitation could be planned better (Feys et al., 2000). Many researches have tried to determine the variables that best predict outcomes after stroke. Somatosensory evoked potentials (SEPs) and fields (SEFs) are possible variables to study stroke recovery as they reflect the activity of the somatosensory cortex. The somatosensory system has an important role in executing precise movements by providing sensory feedback (Kwon and Lee, 2014). Because of the tight connection between sensory processing and movement production, somatosensory activation is important in motor recovery. Abnormal activation of somatosensory cortex contributes to motor dysfunction. The importance of somatosensory input in motor output is evident, as afferent somatosenory input can modulate motor cortex activity by direct modulation of motor cortex inhibition (Favorov et al., 1988). Somatosensory responses are easy to measure and do not require active involvement of the patient.

SEPs can be recorded with electroencephalography (EEG) which detects the electrical potential on the scalp and is useful method for investigating the human somatosensory system. Another noninvasive technique for investigating the brain is magnetoencephalography (MEG) which was introduced in the late 1960s by James Zimmerman (Hämäläinen et al., 1993). With MEG, the extracranial neuromagnetic fields can be recorded. MEG has advantages over EEG in localizing cortical sources, since the magnetic fields are less affected by scalp, skull and cerebrospinal fluid than the EEG signal is (Singh, 2014). The main advantage of MEG is the good spatial and excellent temporal resolution (Hämäläinen et al., 1993).

SEF responses from the contralateral primary somatosensory cortex (SI) elicited by median nerve stimulation were first reported by Brenner et al. (1978). From then on, many studies of somatosensory evoked magnetic fields (SEFs) elicited by electrical stimulation to the peripheral nerves have been conducted (e.g. Hari et al., 1983; Forss et al., 1994b; Kakigi, 1994; Wikström et al., 1996). Electrical stimulation is easy to apply and it produces clear and strong responses, but it is however a mixed nerve stimulation, stimulating both motor and somatosensory nerves. Therefore, various mechanical stimuli such as tapping, vibrating and airpuffs, which are more natural, pure tactile stimulations, have been introduced. Several studies (e.g. Forss et al., 1994b; Wikström et al., 1996; Hari and Forss, 1999; Hoechstetter et al., 2001; Simões et al., 2001; Druschky et al., 2003b; Karageorgiou et al., 2008) have shown that tactile stimulation of a finger evokes responses in the contralateral primary somatosensory

cortex (SI) 20–300 ms and in the contralateral secondary somatosensory cortex (SII) 45–150 ms after the stimulus onset. Moreover, such a stimulus also evokes a response in the posterior parietal cortex (PPC) around 70-110 ms after the stimulus onset (Forss et al., 1994a). It is easily mixed with the late SI-response but the source of it is located in the postcentral fissure. In addition, an ipsilateral response in SII 60–125 ms after the stimulus onset is typically evoked. There are also other sources of activation to somatosensory stimulation, but they are more variable and therefore seldomly reported.

While evoked responses to electrical and tactile stimulation have been studied in great detail, the proprioceptive system has not been widely investigated. Proprioceptive stimulation is difficult to produce in a systematic manner and more importantly without tactile contamination. However, it is one of the most important human somatosensory modalities because it adjusts movement force, speed and direction as well as the body position. Proprioception is the awareness of the body in space and it allows us to walk without falling over. The first reported study on SEFs following passive finger movement was done by Xiang and colleagues (1997). Since then, a few more studies (Lange et al., 2001; Druschky et al., 2003b; Alary et al., 2002; Onishi et al., 2013; Sugawara et al., 2016) have shown that passive movement of a finger elicits SEFs in contralateral somatosensory cortex 20-500 ms after the movement onset.

SEFs elicited to tactile or median nerve stimulation in stroke patients have also been studied. However, only a few studies (Wikström et al., 2000; Gallien et al., 2003; Huang et al., 2004; Tecchio et al., 2006; Forss et al., 2012; Mäkelä et al., 2015; Druschky et al., 2003a) in stroke patients have taken into account the follow-up dimension. The studies have shown that stroke modifies cortical excitability both in the affected and in the unaffected hemisphere and patients often show a reduced activity in the affected hemisphere. Reduced SEF amplitudes in the acute phase are more often associated with poor than good functional outcome.

In the present study, the SEFs elicited by tactile stimulation and passive movement of right and left index fingers are analyzed in 23 stroke patients at acute phase and during one-year recovery.

1.1 Aims of the study

The general aim of this thesis was to study somatosensory cortex activity in stroke recovery at 1–7 days (T0), 1 month (T1), and 12 months (T2) after the stroke. The dataset used in this work were measured and collected by Parkkonen and colleagues (2015; 2017). The specific aim was to quantify magnetic activity to tactile and passive stimulus by defining peak amplitudes of evoked responses and calculating a somatosensory evoked response energy within a specific time window. The goal was to address the following three questions:

- Whether the strength of somatosensory cortex activation increases from T0 to T1, and further to T2.
- Whether the strength of somatosensory cortex activation of the affected hemisphere (unhealthy hemisphere) is smaller than that of the unaffected hemisphere (healthy hemisphere).
- Whether the strength of somatosensory cortex activation of stroke patients is smaller than that of control subjects.

2 Background

2.1 Somatosensory system and somatosensory cortex

The human nervous system is divided into the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS consists of the brain and the spinal cord and the PNS includes the rest of the nervous system such as spinal ganglia, spinal nerves, cranial nerves, the peripheral nerves. Cranial nerves innervate functions of face and head area and are synapting in the brainstem. Spinal nerves carry signals between the brain, the spinal cord and the body. Each spinal nerve is attached to the spinal cord by a dorsal sensory root and a ventral motor root. Peripheral nerves are motor and sensory nerves that connect the brain and spinal cord to the entire human body. Motor nerves send impulses from the brain and spinal cord to all of the muscles in the body (an efferent nerve). Sensory nerves send impulses from the muscles back to the spinal cord and the brain (an afferent nerve).

2.1.1 Somatosensory pathways

The somatosensory system is comprised of two major components: the dorsal column-medial lemniscus system and the anterolateral system. The first one is a major route for touch and proprioceptive information and the latter one for pain and temperature information by which the information ascends to the brain (Bear et al., 2016). These systems give humans the ability to identify different shapes, textures and weight of objects, to detect potentially harmful factors, and estimate the internal and external forces affecting the body (Purves et al., 2004). Below, the dorsal column-medial lemniscus pathway is described more in detail.

Most of the sensory receptors in the somatic sensory system are mechanoreceptors which lie in the skin and underlying tissue. They are sensitive to physical distortion such as bending or stretching. Touch is mediated via four types of mechanoreceptors; Meissner's and Pacinian corpuscles, which are rapidly adapting receptors and detect changes in texture and Merkel's cells and Ruffini's corpuscles, which instead are slowly adapting receptors and reacting to continuous touch and pressure. (Bear et al., 2016)

The information from these four receptor types travels to the cerebral cortex typically through three sensory neurons (Fig. 1). The first sensory neurons bring the information from the mechanoreseptors to the spinal cord through the dorsal roots. The axon enters the ipsilateral dorsal column which carries the touch information to the second-order neurons (dorsal column nuclei) in the medulla. From the dorsal column nuclei the information travels through a white matter tract called the medial lemniscus to the thalamus. The medial lemniscus axons reach the ventral posterior (VP) nucleus of the thalamus, where they synapse with the third-order neurons. Thalamic neurons of the VP nucleus then project to specific regions of primary somatosensory cortex (SI) and other cortical areas. (Bear et al., 2016)

The dorsal column-medial lemniscus pathway is a crossed pathway which means that each side of the brain is receiving information from the opposite side of the body. The information travels along the ipsilateral side until the second sensory neuron

crosses over to the opposite side at medulla. Thus, touch information from the right side of the body is represented in the activity of cells in the left somatosensory cortex. (Bear et al., 2016)

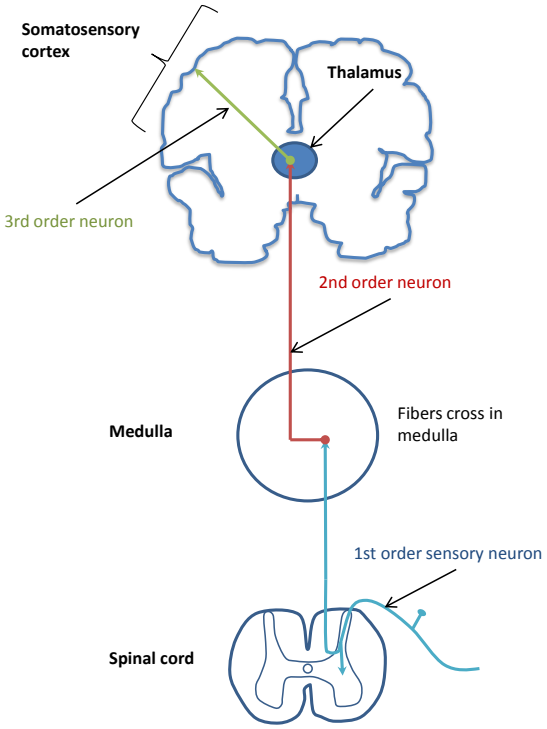

Figure 1: The dorsal column-medial lemniscus pathway.

2.1.2 Primary somatosensory cortex (SI)

The primary somatosensory cortex (SI) is located in the parietal lobe. It lies on the bottom of the central sulcus and at the postcentral gyrus (Fig. 2). It consists of Broadmann areas 3a, 3b, 1, and 2. In fact, area 3 is generally considered the primary area of the somatosensory cortex. Area 3b specifically responds to basic touch sensations, while area 3a is concerned with the sense of body position (proprioceptive information). Area 3 receives the majority of somatosensory input directly from the thalamus. The information flows mainly from areas 3a and 3b to areas 1 and 2. Area 1 is mainly receiving texture information, while area 2 processes the size and shape of objects. Areas 1 and 2 are also sensitive to the direction of stimulus movement across the skin. Further, area 2 is involved in proprioception. Lesions in any of these areas of somatosensory cortex impair somatic sensation. For example lesions in area 3b cause widespread deficits in tactile sensation and lesions in area 1 and 2 produce deficiencies in discriminating the texture, size and shape of objects. (Bear et al., 2016)

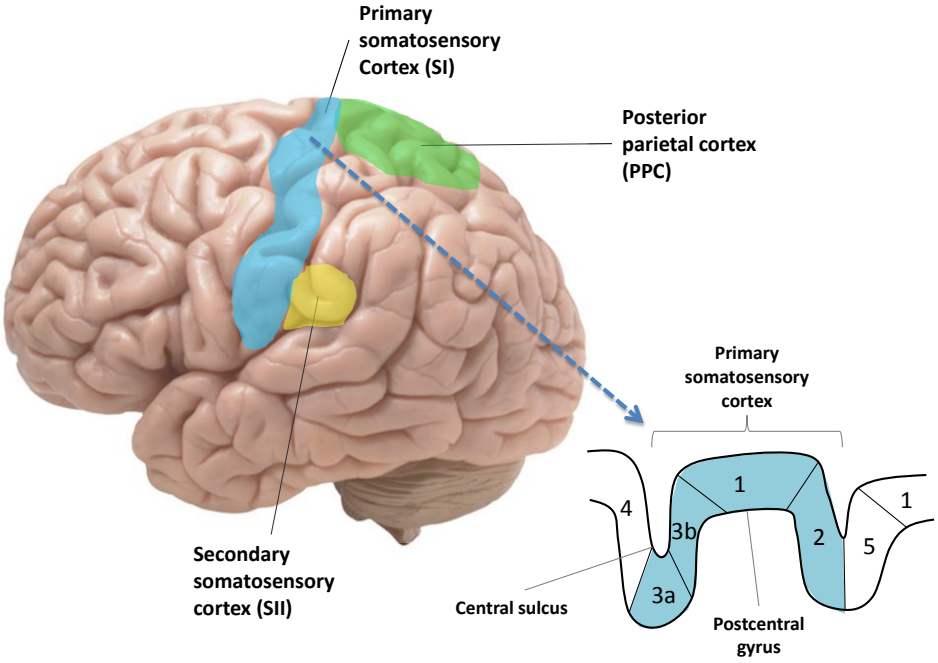

Figure 2: The anatomical locations of the primary somatosensory cortex (SI), secondary somatosensory cortex (SII) and posterior parietal cortex (PPC). SI includes Broadmann's areas 3a, 3b, 1, and 2 and PPC contains areas 5 and 7. Modified from Purves et al. (2004).

Each of the four areas of the primary somatosensory cortex is arranged such that a particular location in that area receives information from a particular part of the body. This arrangement is called somatotopy. Each area in SI (Broadmann 3a, 3b, 2, and 1) has its own somatotopic map where the full body is represented. Because some regions of the body are more sensitive than others and for example more important for tactile discrimination, such as the fingertips and lips, they require a larger representation area in the cortex to be able to process the sensation. Thus, the somatotopic maps are distorted such that the highly sensitive regions of the body have a disproportionate amount of space compared with less sensitive body regions. If a body part, such as a finger, is amputated, neurons responding to stimulation of adjacent fingers (or body parts) will reorganize. This can also happen as the result of increased use of certain region of the body. (Bear et al., 2016)

2.1.3 Secondary somatosensory cortex (SII)

The secondary somatosensory cortex (SII) is located in the upper lip of the lateral (Sylvian) fissure. SII receives connections from the primary sensory cortex (SI) and from the thalamic nuclei, in particular from the ventro-postero-inferior nucleus (VPI) and from the SII of the other hemisphere. It is connected directly to all somatosensory

areas except area 5. Unlike SI, which responds to sensory stimuli almost entirely contralaterally, some of the SII neurons receive input from both sides of the body. Thus, SII is activated bilaterally with unilateral stimulation. SII is also organized somatotopically in which the hand and the face representations occupy most of the total area. However, the receptive fields of neurons in SII are larger and more overlapping than in SI. Thus, the spatial separation of SII is not as good as in SI. (Burton, 1986; Simoes and Hari, 1999; Reed, 2002)

The functional role of SII in tactile perception is not certain. It has been considered that SII plays a role in higher order functions including tactile object recognition, sensorimotor integration, attention, learning and memory (Chen et al., 2008). In humans, lesions to this area may impair texture and shape discrimination. In addition it is believed that SII is critical for coordinating sensorimotor tasks involving multiple body parts or both tactile and motor actions. (Reed, 2002)

2.1.4 Posterior parietal cortex (PPC)

The posterior parietal cortex consists of Brodmann areas 5 and 7 and it is located directly posterior to the sensory cortex in the superior and inferior parietal lobes (Fig. 2). The area receives connections from the primary and secondary somatosensory cortices as well as from other parts of the brain. However, it is not a pure somatosensory association area; it is concerned also with visual stimuli, movement planning, and even a person's state of attentiveness. The neurons of PPC have large receptive fields and their response to several types of inputs are involved in complex associations. The PPC is important for spatial perception, precise body image, and the learning of tasks involving coordination of the body in space. Thus, damage to the area can yield some bizarre neurological disorders. Probably the most well-known disorder caused by a lesion in the right PPC is neglect syndrome. Patients with neglect cannot attend or orient to external stimuli in left hemisphere Another well-known disorder is agnosia. That means that the patient is not able to recognize common objects by touching them although their simple sensory skills are normal. Lesion in the right PPC can also cause anosognosia, which impairs a person's ability to understand and perceive his or her illness. (Bear et al., 2016; Purves et al., 2004)

2.2 Magnetoencephalography

Magnetoencephalography (MEG) is a non-invasive brain imaging method that measures the magnetic fields generated by the electric neuronal activity of the brain. With MEG, brain activity can be measured as a result of sensory stimuli such as sound, touch, or light, or even when no stimuli are given. MEG measures directly brain functioning, unlike functional measures such as fMRI and PET that uses the metabolism of the brain to determine brain function. (Hämäläinen et al., 1993)

2.2.1 MEG instrumentation

The MEG device consists of a helmet-shaped sensor array (Fig. 3). The subject's head is positioned inside to the helmet so that the sensors are able to pick up on

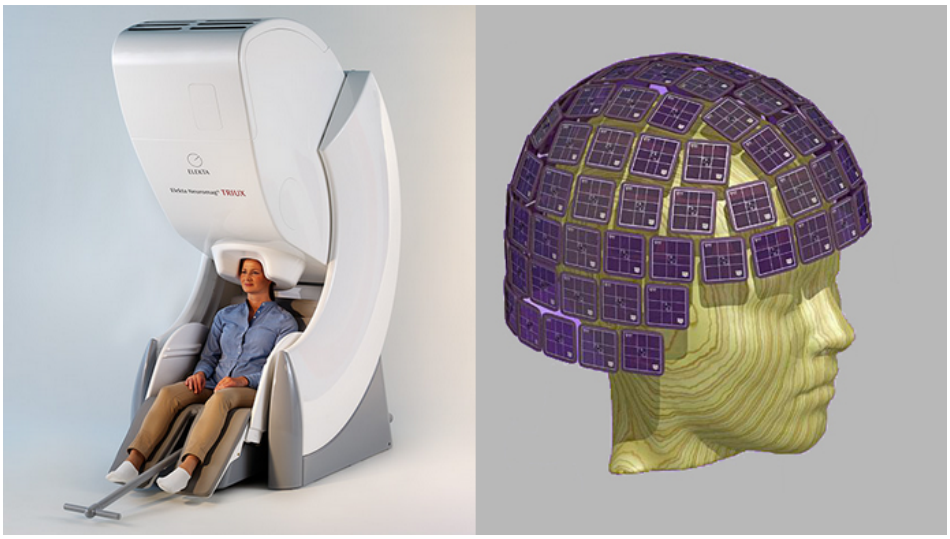

Figure 3: Left: the Elekta Neuromag MEG system. Right: SQUID sensors; 306 independent measurements channels organized in channel-triplets on 102 silicon chips. Each silicon chip includes two planar gradiometers and one radial magnetometer.

extremely weak magnetic fields produced within the subject's brain. The magnetic fields due to brain activity are typically in the order of 50-500 fT (10^{-15} T), about 100 million times weaker than the earth's static magnetic field (10^{-5} T). Thereby, it is not simple to record these extremely small neuromagnetic fields and on the other hand suppress the external magnetic noise. The only sensor that offers sufficient sensitivity for the measurement of these tiny fields is the superconducting quantum interference detector (SQUID). A gradiometric superconducting flux transformer are connected to the SQUIDS to remove environmental noise during measurements. For still better rejection of external magnetic noise the MEG measurements are carried out inside a magnetically shielded room. SQUIDs operate in an extremely cold environment, which is achieved by using liquid helium with a temperature of 4.2 K (-269°C). (Hämäläinen et al., 1993; Singh, 2014; Parkkonen, 2010)

There are different configurations of flux transformers: a magnetometer is a single pick-up coil which measures the magnitude in one point and is therefore more vulnerable to external noise. However, gradiometers which measure a gradient of the magnetic field, are not sensitive to distant sources. It is because of the field, produced by distant sources, changes very little between two adjacent points (very small gradient), in which case these sources are hardly visible in the gradiometric signal. The gradiometer includes two coils and can be arranged in several ways to detect the magnetic field spatially differently. (Parkkonen, 2010)

During the data collection, the Elekta Neuromag MEG (Elekta Oy, Helsinki, Finland) was used. The system's coil configuration combines 204 planar gradiometers and 102 magnetometers for a total of 306 independent channels.

2.2.2 MEG vs. EEG

MEG is closely related to electroencephalography (EEG) which measures electrical potential differences on the scalp whereas MEG measures the magnetic field outside of the head. In both methods, the measured signals are generated by the same synchronized neuronal activity in the brain (Fig. 4). (Hämäläinen et al., 1993)

The main advantage of MEG and EEG, in addition to non-invasiveness, is excellent time resolution. The time resolution is in the millisecond range which is better than in any other non-invasive neuroimaging technique. The very high temporal resolution of MEG and EEG allows to follow the rapid changes in brain cortex activity. (Hämäläinen et al., 1993)

However, EEG detects currents that are tangential and radial to the surface of the scalp, whereas the MEG is sensitive only to tangential currents. But on the other hand, MEG has an excellent spatial resolution which is better than that of EEG. This is due to the fact that scalp, skull and cerebrospinal fluid do not distort the magnetic fields as much as the EEG signal. MEG fields pass through the head without any distortion. This is a significant advantage of MEG over EEG. The MEG sources can be localized with 2-3 millimeter precision whereas EEG source with 7-10 mm precision. (Singh, 2014)

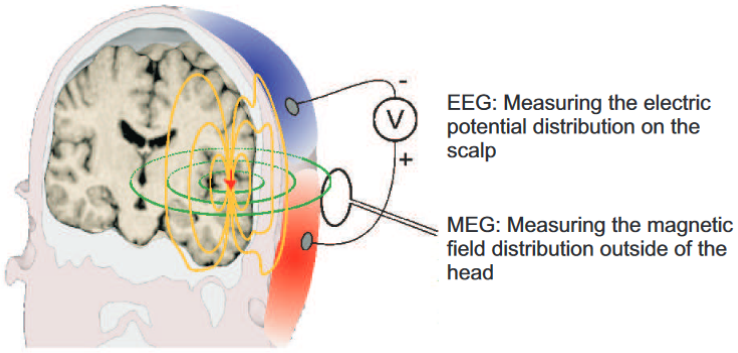

Figure 4: The red arrow represents an electrically active neuron population which produces scalp potentials (red and blue shadings) and extracranial magnetic fields (green lines). EEG records the scalp potentials whereas MEG measures the magnetic field. (Parkkonen, 2009).

2.2.3 Neural basis

The cerebral cortex is a few millimeter thick layer of the brain that covers the outer portion of the cerebrum. It is often referred to as gray matter. It consists of folded bulges called gyri that create deep fissures called sulci. If the brain's outer layer is flattened out it would cover the size of an office desk (about 2 500 cm^2). (Hämäläinen et al., 1993)

The interior of the cerebrum is called white matter. It comprises nerve fibers that bring information to and from the gray matter. It forms connections between different

cortical areas as well as between cortex and other brain structures (Hämäläinen et al., 1993). The white matter does not directly interest us here because MEG signals are due to currents in the gray matter.

The main building blocks of the brain are neurons and glial cells. Although there are roughly 85 billion neurons and approximately the same amount of glial cells in the adult human brain, the neurons are responsible for most of the unique functions of the brain. A neuron consists of a cell body, dendrites and an axon, see Fig. 5. The dendrites are the neuron's input, picking up information from other neurons and sending it to the cell body whereas the axon is the neuron's output passing information to other neurons, muscles or glands. The axon extends from the cell body and ends to a contact with a dendrite of another neuron. The end of the axon is called axon terminal and the point of contact with the dendrite of the other neuron is called synapse. The cell bodies, dendrites and axon terminals of neurons are located in the gray matter while the white matter consists of myelinated axons and glial cells. (Bear et al., 2016)

The dendrites of a single neuron are collectively called a dendritic tree and it functions as the antenna of the neuron. A dendrictic tree has typically thousands of synapses from other neurons. The wide variety of shapes and sizes of dendrictic trees are used to classify different groups of neurons. MEG signals are produced mainly by the dendrites of pyramidal neurons that are located in the gray matter (Hari, 1990). (Bear et al., 2016)

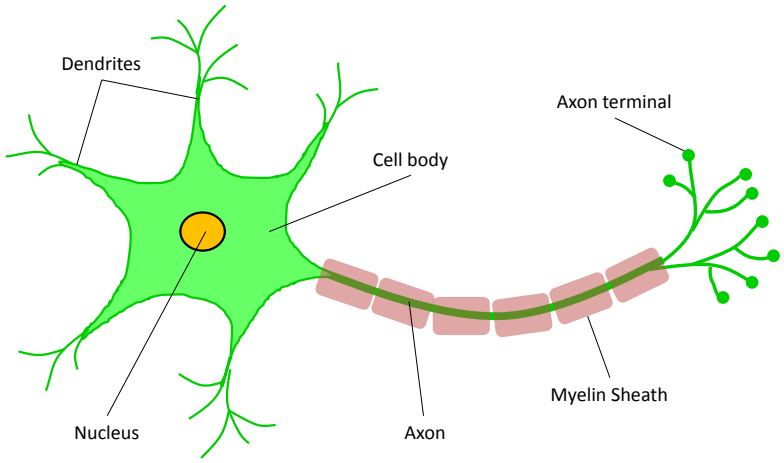

Figure 5: Basic parts of neurons.

Information transfer in the brain occurs between neurons, which communicate by sending electrical and chemical impulses to each other in the synapse. The information travels along the axon of the neuron and finally reaches the synapse. This information current is called a presynaptic potential or an action potential. It is short-lived and biphasic with a time span of approximately 1 ms (Hämäläinen

et al., 1993), as shown in Fig. 6. At the synapse, the arrival of the electrical action potential results in the release of chemical compounds which bind to specific receptors. The receptors then open the associated ion channels resulting in the generation of a postsynaptic potential in the postsynaptic neuron (in the dendrite). The postsynaptic potential is slow compared to the presynaptic; it is monophasic and it may lasts up to tens of milliseconds. The postsynaptic current of a single neuron produce a very small magnetic field. In order that MEG can detect the magnetic fields outside the head, thousands of neurons must be active simultaneously to give rise to fields large enough. Action potentials do not usually generate fields that are measurable by MEG. This is due the fact that action potentials can cancel each other out by reason of their short time spans and biphasic nature. (Hämäläinen et al., 1993; Parkkonen, 2009)

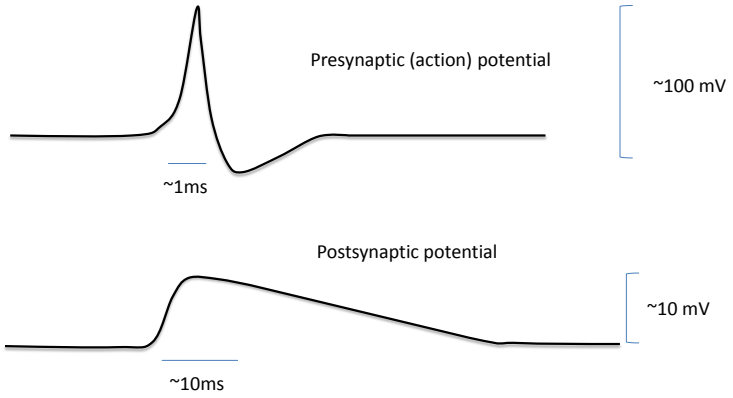

Figure 6: The faster presynaptic action potential and the slower postsynaptic potential. Modified from Hämäläinen et al. (1993).

The current density produced by neuronal activity can be divided into two components: to primary current and to volume current. The primary current flows mainly inside and the volume current in the surrounding medium, as shown in Fig. 7. Because the primary current is restricted in a narrow intracellural area whereas the volume current is spread out in an extracellural area, the current density of the primary current is clearly higher than that of the volume current. Hence, the MEG signal is generally caused by the postsynaptic primary current, even though the magnetic field is generated from both the primary and volume currents. By finding the primary current, the source of brain activity can be located. (Onozuka and Chen-Tung, 2008)

The orientation and location of the postsynaptic current have an impact on the MEG signal. In a perfectly spherical conductor (as an ideal head), radial currents do not produce net magnetic field outside of the head and thus, only tangential

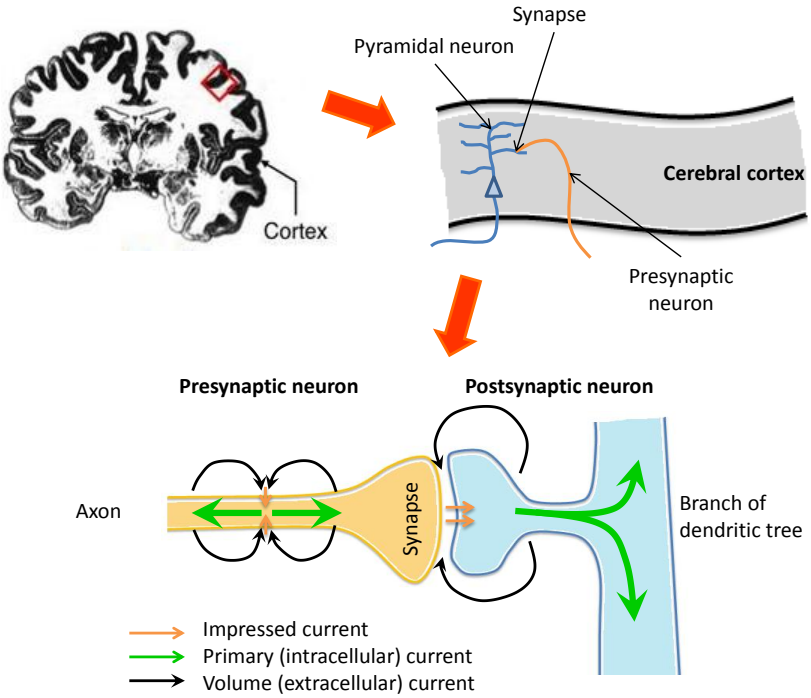

Figure 7: Origins of MEG signals. A synapse at a dendritic spine of pyramidal cell and the associated electric currents. The magnetic field is generated from the volume and the primary currents.

currents can be detected by MEG measurement. Consequently, MEG measures mainly activity from the fissures of the cortex but fortunately, all primary sensory areas of the brain (auditory, somatosensory, and visual) are located within fissures. (Hämäläinen et al., 1993)

2.3 Somatosensory evoked responses

The somatosensory system may be explored by means of somatosensory evoked potentials (SEPs) and somatosensory evoked magnetic fields (SEFs). SEPs are recorded with EEG which detects the electrical potential on the scalp whereas SEFs can be recorded with MEG which detects the extracranial magnetic field. Both are generated by the nervous system in response to sensory stimuli. They are produced by currents created in the cerebral cortex.

SEPs are used for clinical diagnosis in some patients with neurologic diseases, whereas SEFs are used mainly in research. Different features of SEPs and SEFs can be measured, such as peak latencies, amplitudes, generator areas and waveform morphology. SEP responses are typically named by their polarity and usual peak latency in the normal population. For example, N20 is observed as a vertex-negative deflection that typically peaks at 20 milliseconds after the stimulus. The peak latencies are fairly consistent across subjects but may differ slightly due to the age

or limb length of the individual. However, the amplitudes of the evoked responses show large intersubject variability. (Legatt, 2014)

SEPs reflect both fissural and convexial cortical and subcortical activity, whereas SEFs are generated mainly in fissural cortex. Inhomogeneities in tissue conductivities and structures of the skull are expected to severly affect the electric but not the magnetic field patterns. Thus, the locations and activation strengths of the underlying neural generators can be estimated more accurately for SEFs than for SEPs. (Hämäläinen et al., 1993; Nevalainen et al., 2008)

The present study investigates the somatosensory evoked magnetic fields (SEFs) and thus the literature review focuses on studies of SEFs.

2.3.1 Electrical stimulation

The somatosensory evoked magnetic fields (SEFs) elicited by electrical stimulation to the peripheral nerves have been investigated in great detail. The stimulation sites widely used are the median nerve at the wrist, the common peroneal nerve at the knee, and the posterior tibial nerve at the ankle (Legatt, 2014).

Brenner et al. (1978) were the first to show that repetitive somatosensory stimulation of the median nerve evokes SEF responses localized over the contralateral primary somatosensory cortex (SI). Today, it is well known that electrical stimulation elicits four major SEF responses within 100 ms. A typical SEF waveform is shown in Fig. 8, over the contralateral SI, in response to electrical stimulation of the median nerve trunk at the wrist. The earliest response to the electric median nerve stimulation, N20m, peaks at about 20 ms after the stimulation. The next deflection P35m has a peak of opposite polarity and can be detected at 30-40 ms after the stimulus. The third deflection N45m can be seen if short ISIs are used (Kakigi, 1994; Wikström et al., 1996) and it is followed by deflection P60m. All the responses are shown to be located in the contralateral somatosensory cortex (SI). (Huttunen et al., 1987; Tiihonen et al., 1989; Forss et al., 1994b; Wikström, 1999; Ishibashi et al., 2000; Tanosaki et al., 2002)

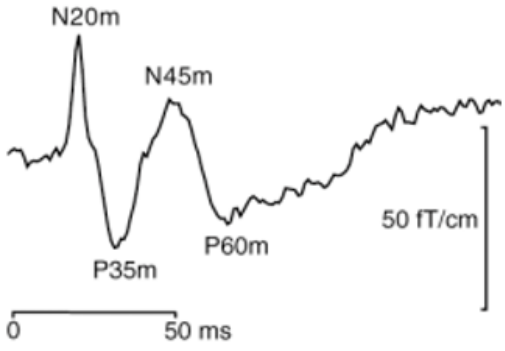

Figure 8: A typical waveform of a channel over SI after median nerve stimulation using an ISI of 1 s. (Wikström, 1999)

Later responses to the electrical median nerve stimulation have been observed at

88-110 ms (P90m) in the contralateral posterior parietal cortex (PPC) (Forss et al., 1994a). Furthermore, activations both in contralateral and ipsilateral secondary somatosensory cortex (SII) are detected at 90-125 ms (P100m) after the median nerve stimulation onset (Forss et al., 1994b; Hari et al., 1983). However, the SII responses peak somewhat earlier and more strongly in the contralateral hemisphere to the stimulated hand than in the ipsilateral hemisphere.

2.3.2 Tactile stimulation

SEPs and SEFs are typically elicited by applying an electrical stimulation to peripheral nerves as described earlier. Electrical stimulation is easy to apply and it produces clear and strong responses but it is however an unnatural stimulation. Therefore, various more natural mechanical stimuli such as tapping, vibrating and airpuffs have been introduced. Airpuff stimulation activates cutaneous mechanoreceptors and elicits clear responses in the main somatosensory cortical areas and is therefore suitable for studies of SEPs and SEFs in cortical areas. (Forss et al., 1994b)

Forss and colleagues (1994b) compared somatosensory evoked fields to airpuff and electric stimuli. The first three deflections to airpuff stimulation peaked at 28 ms, 43-46 ms, and 66-71 ms after the stimulus, clearly later than the corresponding deflection to the electric stimuli (N20-P35-P60). Later responses to airpuff stimulation peaked on average at 98-118 ms from contralateral SII cortex, at 113-125 ms from ipsilateral SII cortex and at 105-110 ms from PPC. The latencies in the later responses arising from areas outside of SI did not significantly differ between tactile and electrical stimulation.

However, Druschky and colleagues (2003b) identified six SEFs main peaks appearing at around 20, 40, 75, 100, 200 and 300 ms following air pressure tactile stimulation. All the components were located in the contralateral primary sensory cortex (SI). However, not all of the components were distinguishable in all subjects, thus the total number of main SEF deflections varied between three and six among subjects. The first deflection (T1-20ms) had the smallest amplitude and it was identified only in three out of 12 subjects. The second deflection (T2-40ms) was the most stable deflection and was present in all subjects at peak latencies in the range of 30–51 ms. The later SEF components (T4-T6) were sometimes merged into one or two broad-based deflections with multiple or not clearly distinguishable peaks. Compared to the other studies, Druschky and colleagues (2003b) did not detect any deflections outside SI probably because they used a relatively short interstimulus interval (1000±100 ms). It is known that responses from PPC and SII region require an ISI of several seconds, possibly even longer than 5 s (Wikström et al., 1996).

In general, several studies have shown that a tactile stimulus to a finger evokes activation of the contralateral SI 20-300 ms after stimulus onset. The main deflection peaks at 40 to 60 ms. Contralateral activation of SII occurs between 45 and 150 ms after stimulus onset with a peak around 100 ms. Furthermore, the tactile stimulus evokes ipsilateral activation in SII between 60 and 125 ms after the stimulus. (Hari and Forss, 1999; Hoechstetter et al., 2001; Simões et al., 2001; Druschky et al., 2003b; Karageorgiou et al., 2008)

Regarding electrical stimulation, the first SEF response has been described to occur at a latency of approximately 20 ms (N20m) and the next one at approximately 30 ms. However, the earliest prominent response to tactile somatosensory stimulation using the air-puff or compressed air is elicited over the contralateral SI at around 40-60 ms. The earlier responses to tactile stimulus are weak and not always detected (Nevalainen et al., 2008). The differences in latencies can be explained by differences in the rise time of the stimuli, the different stimulation sites, and the transduction from mechanical stimulation to a neural response (Mertens and Lütkenhöner, 2000). The longer rise time of the tactile stimulus causes an insufficient synchronization of the SI neural population (Mertens and Lütkenhöner, 2000). The missing early component after tactile stimulus compared with the SEFs to electrical stimulation might be explained not only by the more synchronized activation but also by the different amounts of activated muscle, joint and skin receptors in the different stimulation conditions (Rossini et al., 1996).

2.3.3 Proprioceptive stimulation

Proprioception is one of the most important human somatosensory modalities. While evoked responses to mechanical and electrical stimulations have been studied in great detail, the proprioceptive sense has not been widely investigated. Reports on somatosensory evoked potentials (SEP) following passive movement (Shibasaki et al., 1980; Lee et al., 1986; Mima et al., 1996; Alary et al., 1998) are difficult to compare since the stimulation techniques and data analysis methods are different.

The first reported study on somatosensory evoked fields (SEF) to passive finger movement was made by Xiang et al. (1997). They recorded four main SEF components at the hemisphere contralateral to the moved finger and one component was found in the ipsilateral hemisphere. Thereafter, few more studies about SEF responses following passive finger movement have been made (Lange et al., 2001; Druschky et al., 2003b; Alary et al., 2002; Onishi et al., 2013; Sugawara et al., 2016). The studies indicate that the first deflection (P1) on contralateral hemisphere to passive movement peaks on average around 20-27 ms after stimulus onset. It is not identified in all subjects and it tends to be of small amplitude. Several researchers indicated that the next large deflection (Xiang et al., 1997; Lange et al., 2001; Alary et al., 2002; Druschky et al., 2003b) is considered to include two components (P2, P3) with mean peak latencies around 40-65 ms and 66-100 ms. The latency of the fourth deflection (P4) varies greatly between individuals but it peaks on average around 120-170 ms after the stimulus onset. Moreover, Druschky et al. (2003b) have identified two further deflections peaking on average around 200 ms (P5) and 230 ms (P6) after the stimulus onset. Sometimes the last components were observed as a one combined large deflection including three or two main peaks. However, not all of the deflections are present in all subjects. The ipsilateral deflection has been detected in some subjects to passive movement with mean peak latency around 109-130 ms (Xiang et al., 1997; Onishi et al., 2013; Sugawara et al., 2016).

The SEF source localization (Xiang et al., 1997; Lange et al., 2001; Alary et al., 2002; Druschky et al., 2003b) indicate that the activations of these six first responses

are generated in the contralateral primary somatosensory cortex (SI); more specifically P1 in areas 2 and/or 3a, P2 and P3 in area 4 and P4-P6 in area 3b (Druschky et al., 2003b). Additional contralateral SEF components are identified in some subjects at cortical regions outside SI, including the bilateral perisylvian regions (SII) at 40-470 ms and the contralateral cingulate gyrus at 150-500 ms after passive movement (Druschky et al., 2003b). Furthermore, Alary et al. (2002) identified a later deflection peaking on average at 108-114 ms over the left second somatosensory cortex (SII) for both left and right finger extension and thus they suggest that the human left SII cortex has a predominant role in proprioceptive processing.

Sugawara et al. (2016) recorded SEFs following passive finger movement under three conditions with changing movement range and angular velocity. The study indicated that the amplitude of P1 was dependent on the angular velocity of the movement, whereas the amplitude of P3 was dependent on the duration of the movement.

2.4 Stroke

Stroke is one of the most common neurological diseases and may cause permanent disability. Most common symptoms are hemiparesis, that is inability to move left or right-sided upper and lower extremities and difficulties in producing or understanding speech. It has been estimated that in milder strokes the patients regain about 70% of their original capabilities whereas in severe stroke about 50% of the patient do not show any significant recovery while the other half is getting better. It is not yet known what are the major causes of such difference. Reorganisation of surviving neural networks plays an important role in the recover process. Optimal recovery of movement depends on at least an ability to conserve neural pathways that transport signals into the brain and out of it. Another important thing is neuroplasticity which allows unaffected brain regions to reorganize into effective networks capable of supporting arm and hand function. Failure of either will lead to failure of recovery. (Ward, 2017)

2.4.1 Types of stroke

A stroke is a sudden interruption in the blood supply of the brain. Around 80 percent of all strokes are ischemic and 20 percent are hemorrhagic strokes (Donnan et al., 2008). Hemorrhagic stroke is due to a weakened vessel that ruptures and thus bleeds into surrounding brain tissue. Ischemic stroke is caused by thrombosis or embolism in a cerebral artery, and this cerebrovascular blockage prevents blood flow to a brain area. An important underlying condition for thrombosis is the development of fatty deposits lining the vessel walls (atherosclerosis). The sudden interruption of the blood circulation to the brain causes cessation of oxygen supply for the neurons leading to neuronal death within a couple of minutes.

2.4.2 Brain plasticity

Brain plasticity, also known as neural plasticity, is important in the acquisition of knowledge and skill, and it is closely linked to brain recovery after stroke. Neural plasticity refers to the ability of the neurons to change their form and functioning if the environment alters. In the case of stroke, brain plasticity refers to brain to rewire functions that were once held in damaged areas of the brain over to new, healthy parts of the brain or to ability to grow new synaptical connections to allow preservation of learned skills. In other words, when neurons are damaged by a stroke or brain injury, other neurons may partly take over for them. This adaptive behaviour allows the brain to reorganize in an attempt to recover lost skills. Plastic changes of the brain require several neurophysiological, molecular and genetic changes that are elicited by neuronal death due to oxygen lack. In addition, these changes take place only if action is demanded. Hence, intensive therapy is such a critical element of stroke recovery. (Hara, 2015; Purves et al., 2004)

2.4.3 Recovery and reorganization

Neurological recovery is defined as recovery of neurological impairments and the majority of it occurs within the first 1-3 months. A number of studies have shown that recovery may continue for at least 6 months and 5 % of patients the recovery continues for up to one-year (Bonita and Beaglehole, 1989; Duncan et al., 1992; Kelly-Hayes et al., 1989; Wade et al., 1983). The course of recovery is initially very rapid and after 3 months it continues more slowly (Skilbeck et al., 1983). Functional recovery, which is the ability to do activities, may continue for months after neurological recovery is complete. It has long been known that it is influenced by rehabilitation.

A number of mechanisms are thought to explain the recovery. Some of the early recovery may be due to resolution of edema surrounding the area of the stroke. The edema surrounding the lesion interferes with nearby neuronal functioning and as the edema decreases, the function of these neurons may be reverting. This process may take up to 8 weeks but is usually completed much earlier. (Inoue et al., 1980; Wikström, 1999)

Reperfusion of the ischemic penumbra is another local process which can facilitate early recovery. A focal ischemic injury is surrounded by a region of fair blood flow, known as the ischemic penumbra. Reperfusion of this area causes affected neurons to resume functioning. Besides these, reorganization has been proposed to have a major role in the recovery process. (Huang et al., 2004)

One probable recovery mechanism is the unmasking of existing but functionally inactive pathways. In this theory, the inactive synapses become active when they are released from the inhibitory control of the damaged area. Monkey studies have shown that after digit amputation reorganization of somatosensory cortical maps takes place immediately after the operation (Calford and Tweedale, 1991). This rapid change suggests that the pre-existing pathways become functional after the experimental lesions. (Huang et al., 2004; Wikström, 1999)

Another recovery option is replacement for lost functions by a functionally related brain area. When large cortical areas are destroyed, there may not be enough

surviving tissue near the damaged area and thus local reorganization cannot take place. In such a situation, representations might shift to functionally closely related but more distant brain regions (Lee and Donkelaar, 1995). For example in monkeys after damage to the primary motor cortex, the supplementary motor area can take over new functions (Aizawa et al., 1991). In addition, sprouting of fibers from surviving neurons and formation of new synapses may contribute to post-stroke recovery (Lee and Donkelaar, 1995). To improve stroke recovery, the challenge is to understand how to optimally modify surviving neuronal networks that could replace the damaged tissue with new solutions.

One of the major changes in the post-stroke brain is an alteration of the excitatory-inhibitory balance. Normally, each of the hemispheres inhibits each other. When another hemisphere gets damaged, the other one is not inhibited, thus the healthy hemisphere strengthens. This increased activation of the healthy hemisphere, in turn, inhibits already the weakened damaged hemisphere possibly through the transcallosal fibers. This change in the excitation-inhibition balance happens within days after stroke. The magnitude of the imbalance seems to positively correlate with degree of motor impairment (Murase et al., 2004).

2.4.4 Somatosensory evoked fields in Stroke

Several studies of somatosensory evoked fields to tactile or median nerve stimulation in stroke patients have been made. Only few studies (Wikström et al., 2000; Gallien et al., 2003; Huang et al., 2004; Tecchio et al., 2006; Forss et al., 2012; Mäkelä et al., 2015; Druschky et al., 2003a) in stroke patients have followed up data. However, the studies are difficult to compare due to different research methods, measurement periods and aims.

Forss and colleagues (1999) identified SI and SII responses from stroke patients to median nerve stimulation. In all patients, stimulation of the healthy hand activated the SI and SII cortices of the healthy left hemisphere. To affected hand stimuli, responses showed large interindividual variability due to the different extents of the lesions. If right (affected hemisphere) SI responses were abnormal, right SII responses were absent, whereas the left SII was active in all patients, regardless of the responsiveness of the right SI and/or SII. These results indicate that the human ipsilateral SII areas are not necessarily dependent on activation of the contralateral SI/SII but may have direct thalamic connections and that the information processing works parallel in the human contralateral SI and ipsilateral SII cortices.

Oliviero and colleagues (2004) and Tecchio and colleagues (2001) have studied SEF components of stroke patients after electrical nerve stimulation in acute stroke phase. Both observed that the stroke patients have reliable N20 and P35 SEF components recorded over their unaffected hemisphere (UH) but only some patients showed a reliable SEF recorded over their affected hemisphere (AH). In turn, Rossini and colleagues (2001) measured patients in a clinically stabilized condition (more than 6 months from stroke) and were able to record the SEF components from the AH from all patients except one. Furthermore, they all detected that N20 and P35 peak latencies were normal on the UH but significantly prolonged on the AH in some

patients. In addition, they observed that patients having severe clinical deficits, did not show identifiable SEF from their AH.

Roiha and colleagues (2011) and Forss and colleagues (2012) have studied SEF responses to tactile finger stimulation in stroke patients within 1 week (T0), at 1 month (T1), and at 3 months (T2) after the stroke. They identified SI and SII responses from both hemispheres. The responses were not found in all patients, however when a SII response was detected, it was always preceded by a SI response. They found that there was a significant main effect of hemisphere in patients. The SI responses were significantly weaker in the affected hemisphere than in the unaffected hemisphere at T0 and at T1 (Forss et al., 2012). Further, Roiha and colleagues (2011) observed that SEFs were smaller in the AH than UH one week (T0) and three (T2) months after the stroke but In contrast, the SI amplitudes did not differ significantly between the hemispheres at T1. In addition, Wikström and colleagues (2000) detected that in some patients the amplitude of SII evoked magnetic field to median nerve stimulus increased significantly from the acute phase to 2-3 months from stroke. Forss and colleagues (2012) observed also that in the patients, SI amplitude or latency did not correlate with any of the functional outcome measures used. In contrast, the contralateral PO (cPO) amplitude, reflecting mainly the SII activation, to the affected hand stimuli correlated significantly with hand function in the acute phase and during recovery; the weaker the PO activation, the clumsier the hand was. At 1 and 3 months, enhancement of the cPO activation paralleled the improvement of the hand function. Gallien and colleagues (2003) discover a relation between lack of SEFs and poor sensory recovery. A high correlation between subcortical lesions and increased SEFs latencies on the affected hemisphere was also found.

It can be concluded that reduced SEF amplitudes in the acute phase are more often associated with poor than good functional outcome. Stroke modifies cortical excitability both in the affected and in the unaffected hemisphere and stroke patients often show a reduced activity in the affected hemisphere. Decreased activation in the affected hemisphere might causes enhanced activation in the unaffected hemisphere due to decreased callosal inhibition. Normally, each of the hemispheres inhibits each other. When another hemisphere gets damaged, the other one is not inhibited, thus the healthy hemisphere strengthens. This increased activation of the healthy hemisphere, in turn, inhibits already the weakened damaged hemisphere (Forss et al., 1999). The increased activity has been detected both in the affected and unaffected hemispheres after stroke (Liepert et al., 2000; Manganotti et al., 2002; Bütefisch et al., 2003) and is probably related to plastic reorganization of the cortex (Jacobs and Donoghue, 1991).

3 Methods

In this part the methods for data collection are described briefly. The data collection was performed by Parkkonen and colleagues (2015; 2017). They studied how passive movement and tactile stimulation modulate motor-cortex excitability in healthy subjects (2015) and in patients after a stroke (2017).

3.1 Patients

The study used data of 23 patients (10 females and 13 males, age 45–78 years, mean 65 ± 2 years) with first-ever stroke in the middle cerebral artery territory causing unilateral upper limb paresis. Clinical details of the patients are shown in Table 1. The patients did not have earlier neurological diseases, mental disorders, neurosurgical operations or unstable cardiovascular condition. More detailed information of the patients can be found in Parkkonen et al. (2017). For further analysis the patients were divided into two groups according to the lesion side. Seven of the patients had a lesion in the left hemisphere thus their right hand was impaired (hemiparesis DX). Respectively, 16 patients had a lesion in the right hemisphere and the left hand was impaired (hemiparesis SN).

22 healthy control subjects (11 females and 11 males, age 42–72 years, mean 59 ± 2.0 years) were included. All volunteers were right-handed and with no history of neurological disorders. The experimental procedures were approved by the Local Ethics Committee of Helsinki and Uusimaa Hospital District. (Parkkonen et al., 2015)

3.2 MEG recordings

The neuronal activity of the brain was recorded by Parkkonen and colleagues (2015; 2017) using a 306-channel whole-head MEG system (Elekta Oy, Helsinki, Finland). During the recordings, the subjects were either sitting or in supine position with the head supported against the helmet-shaped sensor array. The patients were instructed to relax and not to pay any attention to the stimuli. The signals were band-pass filtered between 0.03–330 Hz and digitized at 1000 Hz. For both tactile and passive stimuli around 60 accepted trials were collected for each hand.

The patients underwent the MEG recordings 1–7 days (T0), 1 month (T1), and 12 months (T2) after the stroke.

3.3 Tactile stimulation

Pneumatic diaphragms driven by compressed air were used to deliver tactile stimuli to the fingertips. The duration of the stimuli were 141 ms and it got its peak at 50 ms. The stimuli were given to the tips of both left and right index fingers, alternately with an interstimulus interval (ISI) of 1.5. Therefore, the ISI for one side was 3 seconds. (Parkkonen et al., 2015)

Table 1: Clinical details of the patients. F = female, M = male, R = right, L = left, C = cortical, CS = cortico-subcortical, S = subcortical.

Patient	Gender	Age	Lesion Side	Lesion Site	Lesion Size (cm^3)
1	F	68	R	C	1.78
2	F	59	L	C	0.24
3	F	60	R	CS	24.9
4	M	66	R	CS	71.3
5	M	45	R	CS	84.2
6	F	58	R	CS	31.7
7	F	66	R	CS	4.58
8	M	71	R	CS	26.7
9	M	75	R	CS	35.8
10	M	62	R	CS	21.2
11	M	67	R	CS	218.5
12	M	47	R	CS	149.9
13	F	78	R	CS	55.6
14	M	61	R	CS	124.8
15	M	49	L	CS	3.53
16	M	76	L	CS	2.59
17	F	73	L	CS	2.84
18	M	68	R	S	1.36
19	F	59	R	S	1.95
20	F	75	R	S	13
21	M	64	L	S	1.46
22	F	74	L	S	40
23	M	74	L	S	0.48

3.4 Passive movement

For passive movements, a nurse extended rapidly the subject's index finger and lowered it back to the initial position once every three seconds. Right and left index fingers were stimulated separately. To produce as pure proprioceptive and constant tactile stimulation as possible during the finger lift, the cutaneous tactile stimulation was minimized by covering the middle phalanx with a surgical tape. (Parkkonen et al., 2015)

Timing and amplitude of the movements were kept constant by monitoring them with two separated optical gates. The lower gate was located just above the finger at resting position and the upper gate was located 30 mm higher (Fig. 9). Only movements passing through both gates within 500 ms were accepted as valid trials. Moreover, since the passive movement had already started before the index finger reached the lower gate, the actual onset of the movement was calculated afterwards using an accelerometer signal. Since the accelerometer signal was available only for 17 controls and 16 patients, the averaged lag between the actual movement and the

recorded movement was used for patients lacking the signal.

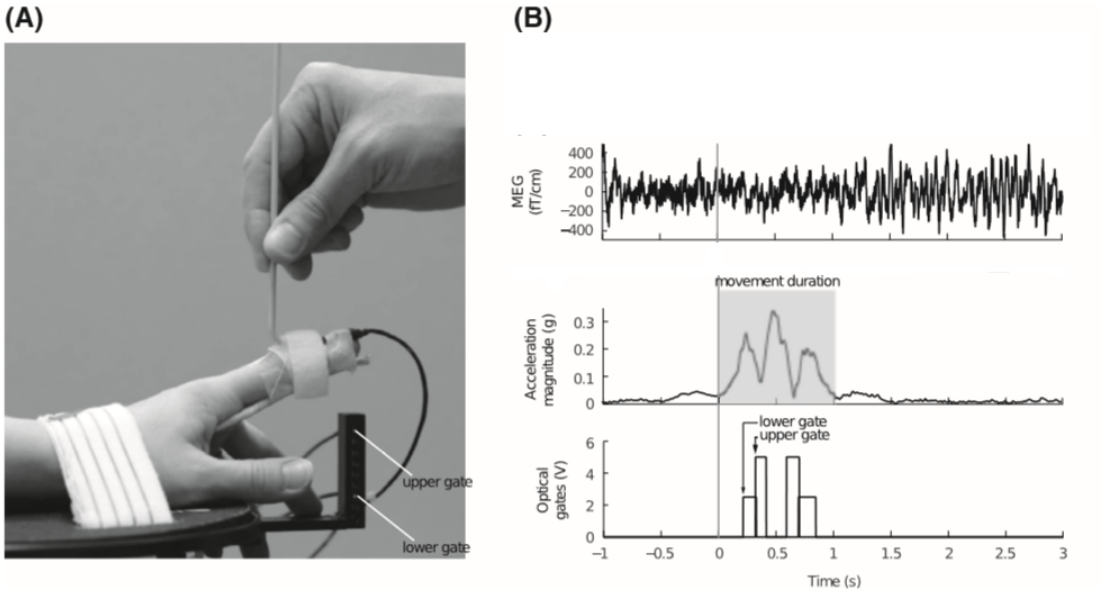

Figure 9: (A) The arrangement for passive movement. (B) Representative signals of one subject during right index finger passive movement. Upper row: MEG signal from a single gradiometer channel. Middle row: magnitude of acceleration. Total duration of movement is highlighted with gray. Bottom row: trigger signals from the lower and upper optical gates. Modified from Parkkonen et al. (2015)

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3.5 Data analysis

3.5.1 MNE software package

The data processing was done using the MNE-python software package. MNE is an academic open-source software package for MEG and EEG data processing. It is named after a method used for solving the electromagnetic inverse problem called minimum-norm current estimates. The software package includes varied analysis tools and workflows for processing MEG and EEG data. It covers preprocessing, source estimation, time-frequency analysis, statistical analysis, and a number of methods to estimate functional connectivity between brain regions. The software consists of three subpackages: the original MNE-C package is based on compiled C code, MNE-Matlab provides basic MNE functionalities in Matlab and MNE-Python is based on Python programming language. All of the versions use the same Neuromag FIF file format, enabling the user to move between the packages easily. Full documentation of the software is available at http://martinos.org/mne. (Gramfort et al., 2014)

The MNE website offers an extensive set of example scripts with typical workflows which can be downloaded as MNE-Python code. The package was used for preprocessing, epoching and averaging the data.

3.5.2 Steps for data analysis

First, the raw data were preprocessed and thereafter epoched and averaged with MNE-Python. Then, appropriate MEG channels were chosen. The averaged data were grand averaged to detect the main responses after the stimulus onset. From the averaged data, maximum peak amplitudes were defined for each subject at each time point and for both healthy and impaired hands. Similarly, the response energy for each subject were calculated. The main steps of the data analysis are shown in Fig. 10 and described in more detail beneath. The processing was done for tactile and for passive-movement data separately.

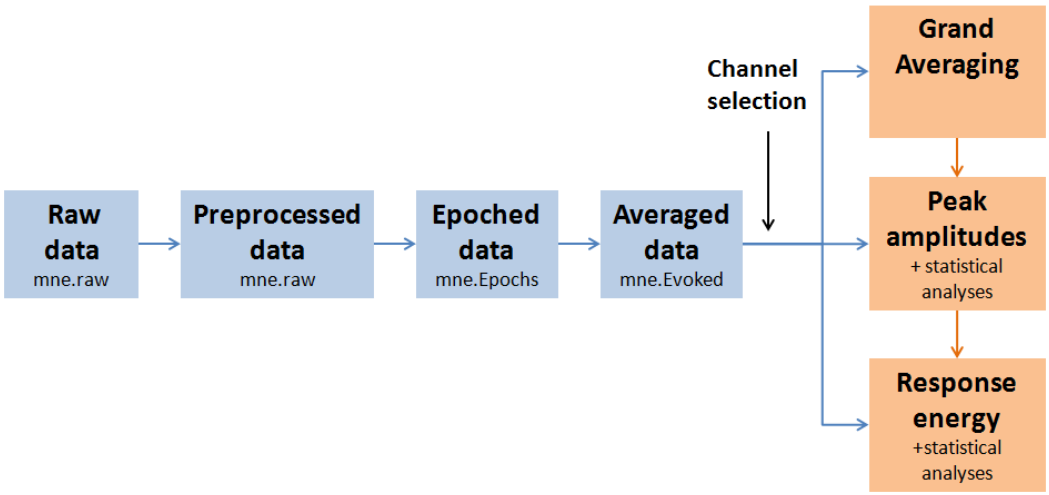

Figure 10: Steps for the data analysis.

3.5.3 Preprosessing

For the removal of external magnetic interference, the raw data were preprocessed with the temporal signal space separation (tSSS) method (Taulu et al., 2004) using MaxFilter software version 2.2.11 (Elekta Oy, Helsinki, Finland). The tSSS method efficiently suppresses external magnetic artifacts from the measured data (Taulu et al., 2004). Furthermore, the head movement correction method implemented also in MaxFilter software was used. The raw data was low-pass filtered with a cutoff frequency of 30 Hz.

3.5.4 Epoching and averaging

Since the objective of the analysis is to investigate how the somatosensory cortex of patients responds to tactile or passive stimuli, the interesting segments of the measurement data are the time intervals around each stimulus event. Rather than looking at the complete set of continuous MEG measurement data, the data were cut into segments around the stimulus events. This process is called epoching. The MEG measurement data includes a trigger channel which contains the timing of each stimulus (event). The epoching can be done with help of that channel. Also the

accelerometer channels for passive movement were used when creating the epochs of passive movement. The epochs made for tactile stimulation collected the data from 400 ms before to 1000 ms after the event. For passive movement, the epochs started 500 ms before and ended 2000 ms after the event. To get meaningful amplitude values, it is important to define a baseline period for the epoch constructor. Baselining computes the mean over the baseline period and adjusts the data correspondingly (Gramfort et al., 2014). For tactile stimulus, the baseline level was determined using a prestimulus period between -300 ms and -100 ms and for passive movement between -500 ms and -300 ms. It is also reasonable to omit noisy epochs by defining rejection thresholds for gradiometers, magnetometers and electrooculography (EOG) channels. The rejection parameters are defined as peak-to-peak values within the epoch time span and thus values higher than the rejection thresholds will cause the epochs to be rejected. The rejection parameters were chosen for each data file separately from the ranges presented in Table 2 (for tactile data) and in Table 3 (for passive data).

Thereafter, the epochs were averaged to form an evoked response. The benefit of averaging is to increase the signal-to-noise ratio due to the random noise being averaged out. At least 50 accepted epochs were averaged for each condition.

Table 2: The interval of rejection parameters for tactile data to remove noisy epochs. The rejection was made for epochs that had higher values than the rejection parameter.

Source	**Rejection parameters**	**Unit**
magnetometers	2.5 – 6.5	pT
gradiometers	0.6 – 1.5	pT/cm
EOG	200 – 900	μV

Table 3: The interval of rejection parameters for passive data to remove noisy epochs. The rejection was made for epochs that had higher values than the rejection parameter.

Source	**rejection parameters**	**Unit**
magnetometers	2.5 – 9.5	pT
gradiometers	0.5 – 1.9	pT/cm
EOG	200 – 1000	μV

3.5.5 Channel selection

Since the evoked response to tactile stimuli and passive movements were known to be generated in somatosensory cortex, the analysis was focused on the planar gradiometer channels above that area. These channels are shown in Fig. 11.

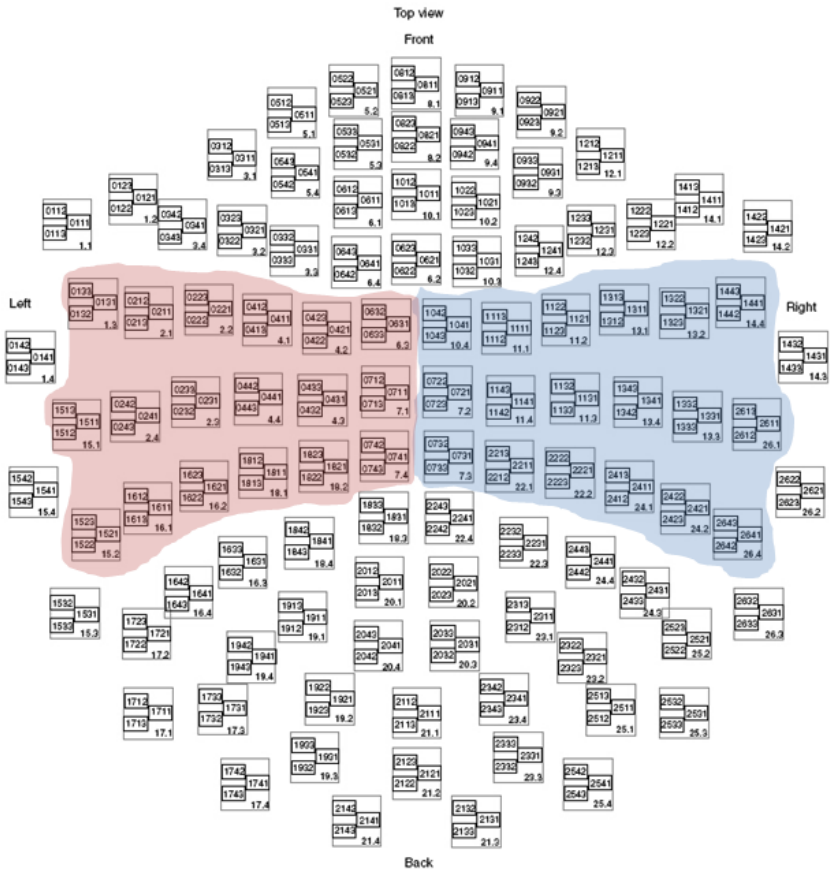

Figure 11: Sensor layout of the whole-head MEG system. The helmet shaped sensor array is flattened into a plane. The channels used for data analyses are highlighted in red and blue.

3.5.6 Grand averaging

Grand averaging helps to observe the main evoked responses after the stimuli and define the time window for calculation of the response energy. It is used to average together the data from multiple datasets. The most common use for this is to create a grand average across subjects. Here, such averages were made separately for control subjects and patients. The left hand and right hand stimulation were also separated into different grand averages. Furthermore, patient datasets were divided to affected and unaffected hand stimulation. Grand averaging was made over patients in each time points T0, T1, and T2.

3.5.7 Peak amplitudes

The peak amplitudes of the responses were picked within certain time windows defined in the grand averaging phase; an early and late window were defined for both

tactile and passive responses. The peak amplitudes were determined only for the contralateral hemisphere with respect to the stimulated hand.

3.5.8 Response energy calculation

To robustly quantify the activity evoked by the stimuli, the area under the event-related potential curve was quantified for each subject separately. The area was calculated as an integral of the absolute value of the waveform. The response energy was calculated in both ipsilateral and contralateral hemispheres with respect to the stimulated hand from 72 gradiometer channels (36 from each hemisphere) as shown in Fig. 11. The areas from 36 gradiometer channels from one hemisphere were summed up and the total magnitude of the stimulus response in the ipsilateral or contralateral hemisphere was obtained.

The response energy measures the total activity elicited in the somatosensory cortices in one hemisphere. Since source modeling could not be performed in this study and thus the sources of the individual evoked responses are not certain, the energy calculation was made to detect the changes in total activity during the stroke recovery. With this method, the accurate source locations or accurate latencies of the responses are not important and thus the response energies of patients and control subjects can be reliably compared.

3.6 Statistical analysis

T-tests were used in this work to compare two means and tell if they are significantly different from each other. *The paired two-sample t-test* was used to compare the response energy or response amplitude in patients for time points T0, T1, and T2. The test determined if the observations in T0 and T1 or T2 are from different distributions with different population means. The paired two-sample t-test was used also when comparing the results of the affected and unaffected hemisphere in patients. *The two-sample t-test* is used when comparing different groups. This test was used when comparing the means of controls and patients. As it is not known if the variances are the same or not, the two sample t-test with unequal variances was used.

4 Results

4.1 Tactile responses

4.1.1 Grand averages

The grand averages were calculated to find when the responses to tactile stimulus appear, what are the reasonable time windows for searching the responses with largest amplitudes and what is a suitable time window for the response energy measurement. The grand averages show that the responses to tactile stimuli occurred within 500 ms after the stimulus onset (see Fig. 12 and 13).

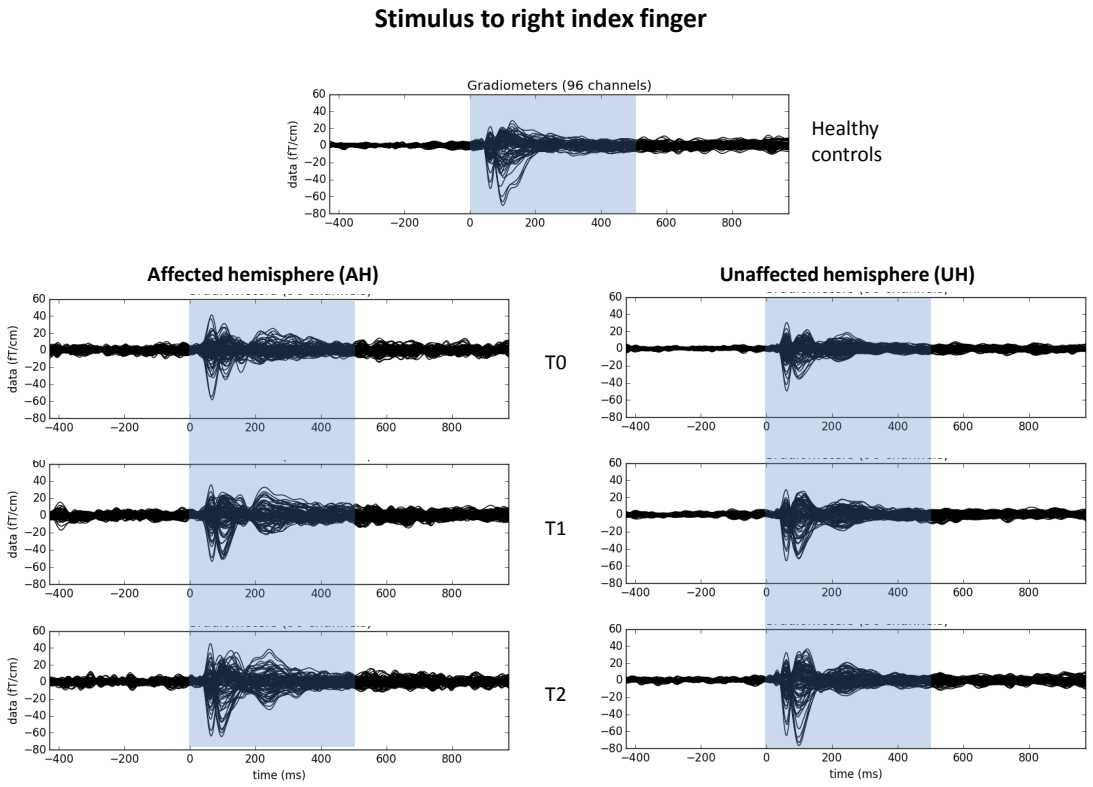

Figure 12: Superimposed grand-average SEF responses recorded from the hemisphere contralateral to tactile stimulus to right index finger. The responses occurred mainly within 500 ms after the stimulus onset.

Figure 14 shows grand average responses to tactile stimulus to the right and Figure 15 to the left index finger, respectively. The insets show enlarged responses from three locations. Grand averages indicate that tactile stimulus to the index finger elicited two main responses over the parietal region in the contralateral hemisphere with respect to the stimulated hand. The responses peaked on average at 60 ms and 100 ms after the stimulus onset. Those were followed by a third response peaking 190–250 ms after the stimulus onset over the contralateral parietal region. The amplitude of the response was low but it was wider than the first two. It was also

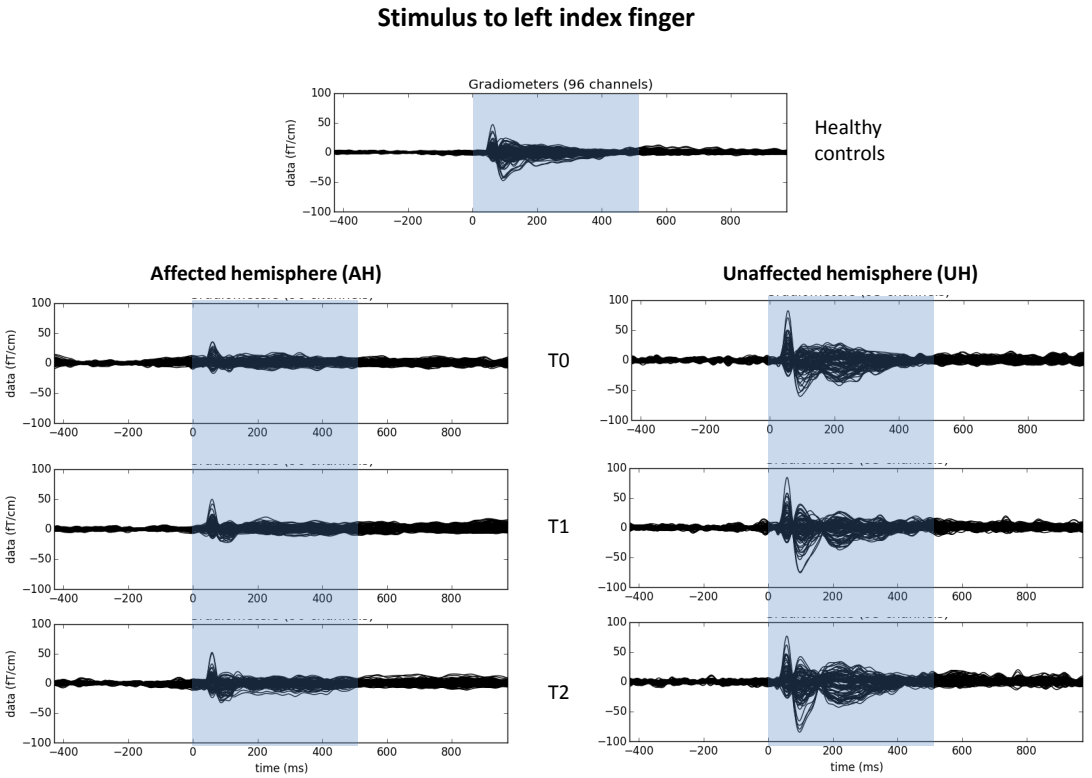

Figure 13: Superimposed grand-average SEF responses recorded from the hemisphere contralateral to tactile stimulus to left index finger. The responses occurred mainly within 500 ms after the stimulus onset.

spatially spread out particularly to the left-hand stimulus. On the ipsilateral side, the main response was peaking on average 100–120 ms after the stimulus to the right hand. The ipsilateral response to the left-hand stimulus was more spread out and not that pronounced.

Even though the source modeling was not made in this study, it is likely that the first response (60 ms) corresponds to the previously reported contralateral SI activity and the second response (100 ms) to the contralateral SII activity.

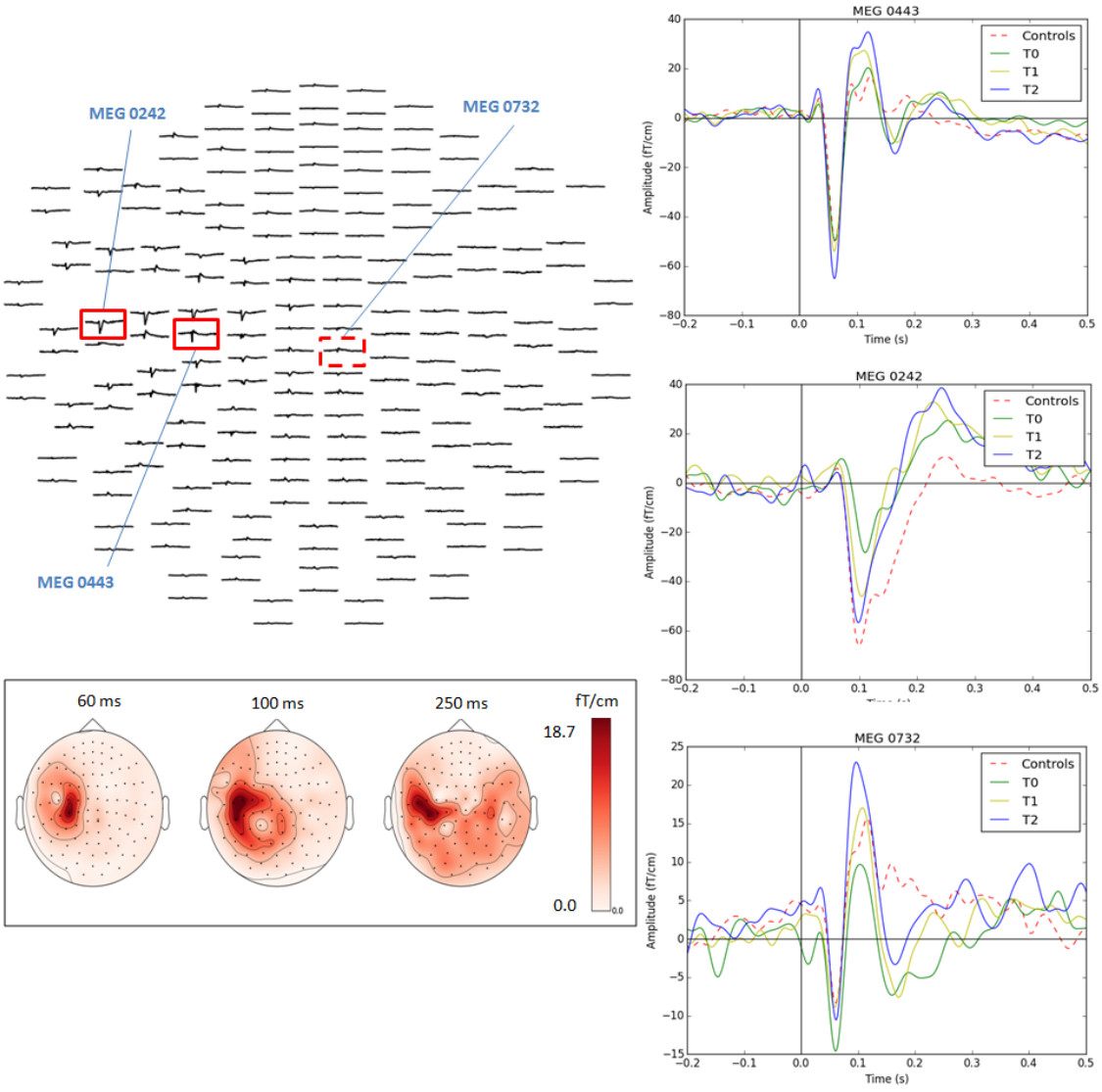

Figure 14: Distribution of the cortical responses of patients and healthy controls to tactile stimulus to the right index finger (healthy hand). The view is from above the head with the nose pointing upwards. The largest responses occur in the frontoparietal planar channels above the contralateral left hemisphere. A small response is detected also in the channel MEG 0732. Enlarged responses from the encircled channels are shown on the right. The picture below shows that early activation occur in the left hemisphere and later on the activation spreads also to the right hemisphere.

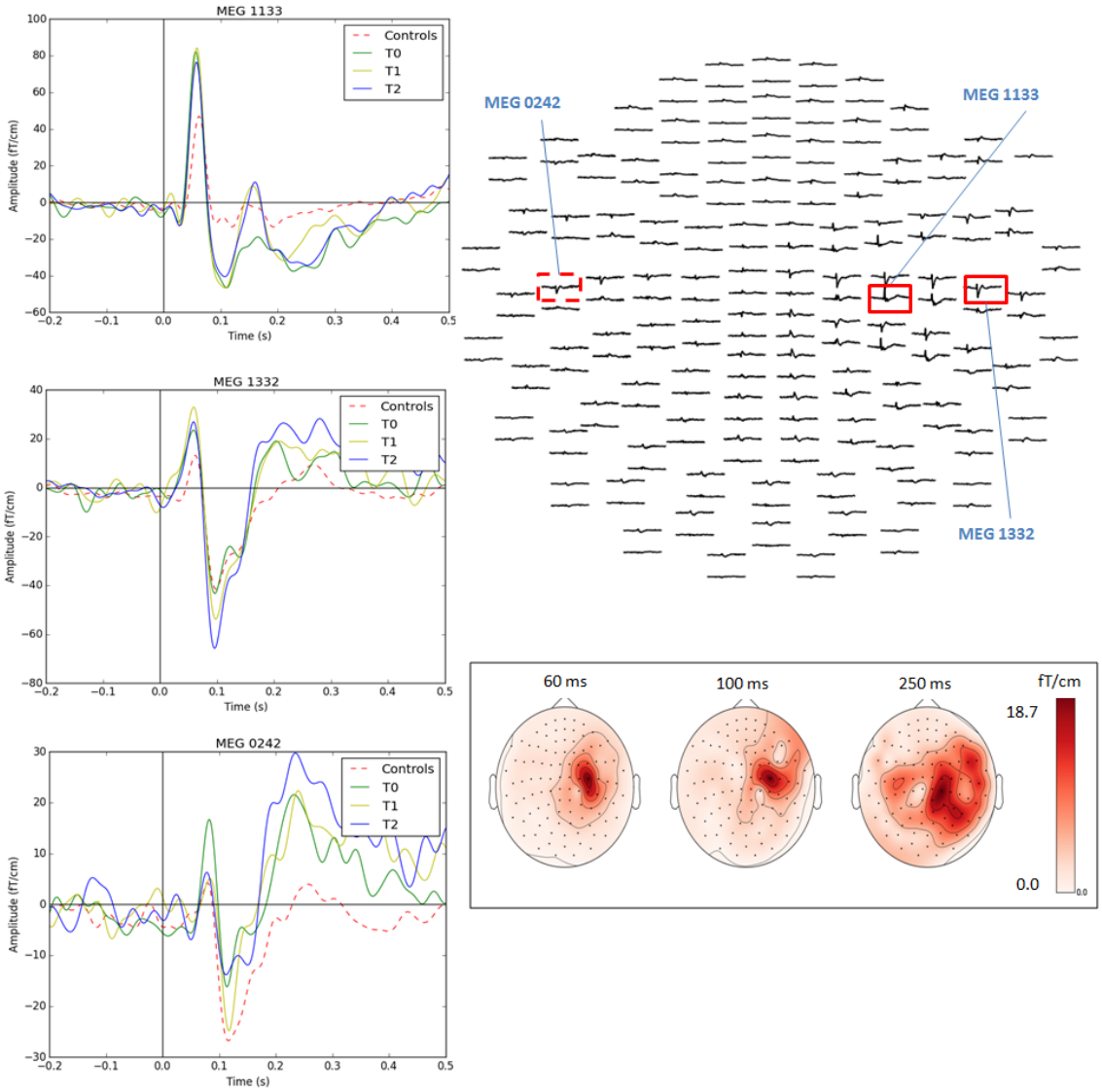

Figure 15: Distribution of the cortical responses of patients and healthy controls to tactile stimulus to the left index finger (healthy hand). The view is from above the head with the nose pointing upwards. The largest responses occur in the frontoparietal planar channels above the contralateral right hemisphere. A small response is detected in the ipsilateral (left) hemisphere. Pictures on the left show enlarged responses from the encircled channels. The picture below shows that early activation occur in the right hemisphere and later on spreads also to the left hemisphere.

4.1.2 Response amplitudes and latencies

As already mentioned when presenting the grand averages, tactile stimulation elicited two main responses in contralateral hemisphere with respect to the stimulated hand. The first deflection peaked on average at 60 ms after the stimulus onset and is thus named in this study evoked response TACT60. The TACT60 peak amplitudes and corresponding latencies were searched in each subject and measurement by calculating the largest amplitude of the response deflection within a time window 40–80 ms after the stimulus onset. The second response peaked on average at 100 ms after the stimulus onset and is named as TACT100 response. The TACT100 peak amplitudes and corresponding latencies were searched within a time window of 80–130 ms. The peak amplitudes and corresponding latencies are shown in Table 4 and Fig. 16. The peak amplitudes on the ipsilateral side were not studied.

Table 4: Mean (+SEM) SEF energies, peak latencies and the corresponding amplitudes of responses to tactile stimulus of index finger. The SEF energies are measured from the both contralateral and ipsilateral side with respect to the stimulated hand. Recordings made at 1–7 days (T0), 1 month (T1), and 12 months (T2) after the stroke. UH = unaffected hemisphere in patients, AH = affected hemisphere in patients.

	1st response		2nd response		Response energy	
	Latency (ms)	Amplitude (fT/cm)	Latency (ms)	Amplitude (fT/cm)	Contralateral (fT/cm)*s	Ipsilateral (fT/cm)*s
Controls	63 ± 1.0	63 ± 3	101 ± 2.1	88 ± 6	214 ± 10	134 ± 6
T0 UH	61 ± 1.3	78 ± 7	100 ± 2.6	88 ± 10	250 ± 19	215 ± 26
T1 UH	60 ± 1.1	86 ± 7	99 ± 2.1	98 ± 7	268 ± 13	225 ± 25
T2 UH	60 ± 1.2	96 ± 9	99 ± 2.8	114 ± 11	297 ± 22	228 ± 21
T0 AH	64 ± 1.8	71 ± 9	107 ± 3.3	55 ± 5	235 ± 26	143 ± 11
T1 AH	66 ± 2.1	68 ± 8	101 ± 2.7	66 ± 6	236 ± 16	158 ± 10
T2 AH	59 ± 1.3	82 ± 9	101 ± 2.9	88 ± 8	275 ± 22	173 ± 12

Temporal evolution

The TACT60 response in the affected hemisphere (AH) peaked significantly earlier at 12 months after the infarct (T2) than at acute phase (T0) (87 ms vs. 92 ms, $p < 0.001$) or at one month (T1) post-stroke (87 ms vs. 94 ms, $p < 0.05$). Similarly, the TACT100 response in the AH tended to peak significantly earlier at T2 than at T0 (101 ms vs. 107 ms, $p < 0.06$).

The amplitudes of the both responses were significantly weaker at T1 than at T2 in the affected hemisphere ($p < 0.05$ for TACT60; $p < 0.01$ for TACT100) In addition, the amplitude of the TACT100 responses were significantly weaker at T0

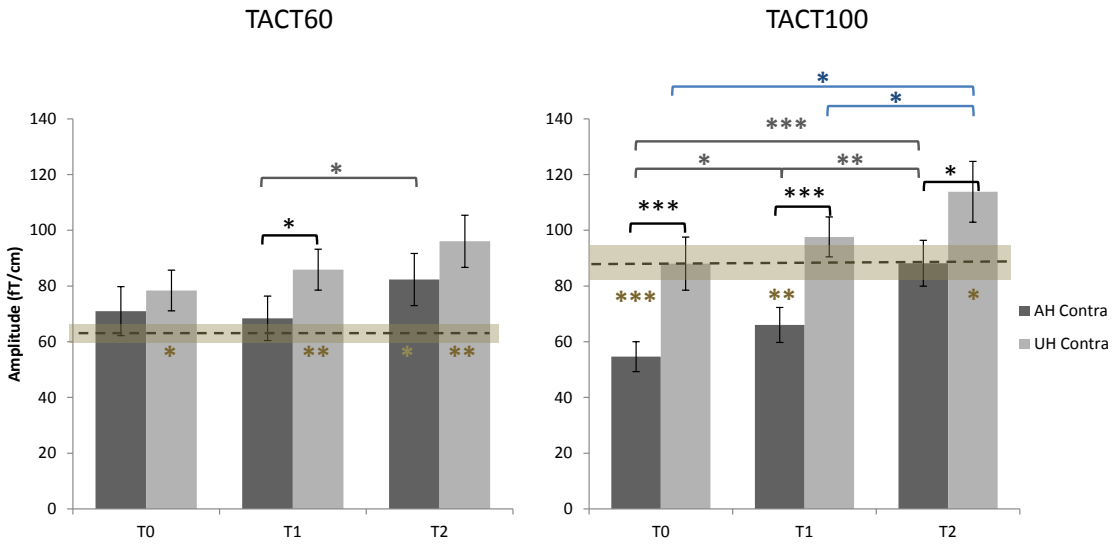

Figure 16: Mean (± SEM) peak amplitudes of TACT60 and TACT100 responses of the patients. AH = affected hemisphere, UH = unaffected hemisphere. The mean amplitudes of the control subjects are shown with dashed brown lines. (* $p < 0.05$ and ** $p < 0.01$ and *** $p < 0.001$ with paired two-sample [comparing the means of different time points, and the means of affected and unaffected hemispheres in patients] or two-sample t-test [comparing the means of controls and patients]).

than at T2 in the both affected and unaffected hemispheres ($p < 0.001$ for AH; $p < 0.05$ for UH).

Affected versus unaffected hemisphere

The TACT60 peaked significantly later in the AH than in the UH at T1 (66 ms vs. 60 ms, $p < 0.05$) and the amplitude of the response was significantly stronger in the UH than in the AH at T1 ($p < 0.05$). The TACT100 tended to peak later in the AH than in the UH at T0 (107 ms vs. 100 ms, $p < 0.065$) whereas the response amplitude was significantly stronger in the UH than in the AH at all time points ($p < 0.001$ for T0 and T1; $p < 0.05$ for T2).

Patients versus healthy controls

The TACT60 peaked significantly earlier in patients at T2 than that of healthy control subjects (59 ms vs. 63 ms, $p < 0.05$). The amplitude of the response was significantly stronger in patients than controls at T2 in the AH ($p < 0.05$) and moreover, at all time points in the UH ($p < 0.05$ for T0; $p < 0.005$ for T1 and T2).

In contrast, the second response TACT100 in the AH was significantly weaker in patients than in controls at T0 and at T1 ($p < 0.001$ for T0; $p < 0.01$ for T1), but the response in the UH was however significantly stronger in patients than in controls at T2 ($p < 0.05$).

The p-values of the statistical analysis are shown in Appendix A.

4.1.3 Response energy

The response energy was calculated to measure the total activity in the somatosensory cortices of one hemisphere elicited by the tactile stimulus to the index finger. The grand averages showed that the responses to tactile stimuli occurred within 500 ms after the stimulus onset. Therefore, the suitable time window for the response energy measurement was 0–500 ms (see Fig. 12).

Temporal evolution

The results, shown in Fig. 17, indicate that the response energy tends to grow from the first (T0) and the second measurements (T1) to the last measurement (T2). The response energy was significantly smaller ($p < 0.05$) at T0 than at T2 in both the contralateral affected hemisphere (AH) and unaffected hemisphere (UH) with respect to the stimulated hand. In addition, the contralateral response energy was significantly smaller at T1 than at T2 in the AH ($p < 0.01$).

Moreover, the response energy was significantly smaller at T0 than at T1 or at T2 in the ipsilateral AH with respect to the stimulated hand ($p < 0.05$ for T0 vs T1; $p < 0.05$ for T0 vs T2) while there were no significant differences between the time points in the ipsilateral UH responses.

Affected versus unaffected hemisphere

The results show that the response energy in the contralateral AH, with respect to the stimulated hand, was significantly smaller than in the contralateral UH at T1 ($p < 0.05$).

In the ipsilateral side with respect to the stimulated hand, the response energy was significantly smaller in the AH than in the UH at all time points ($p < 0.005$).

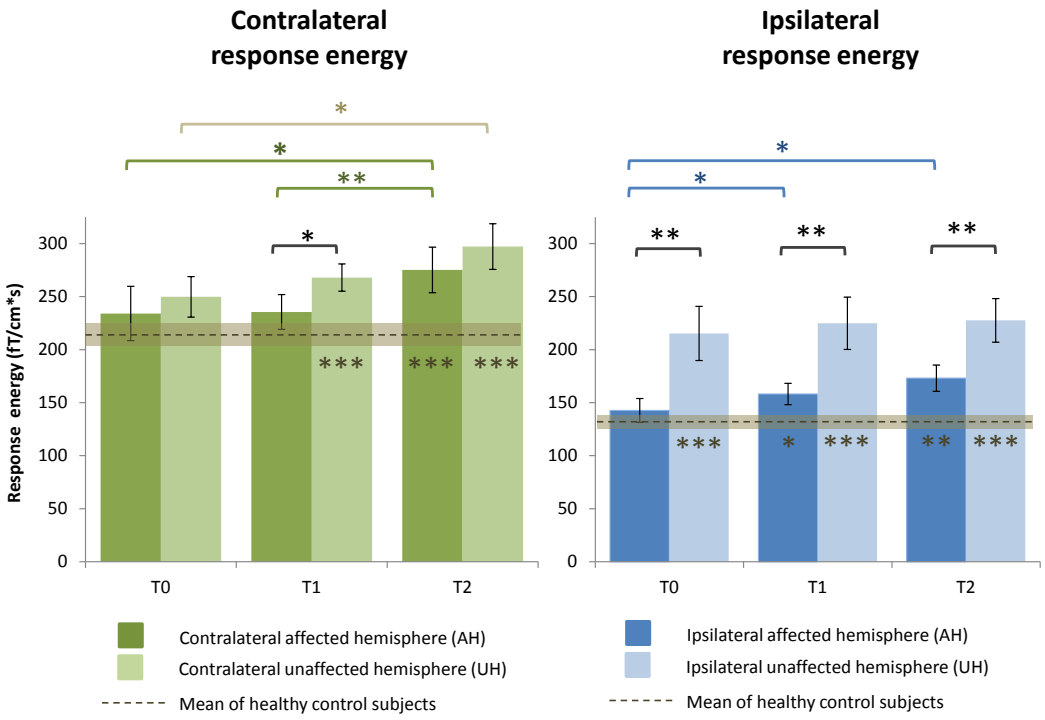

Figure 17: Mean (± SEM) energy at contralateral and ipsilateral responses to tactile finger stimulation of the patients. The mean response energy of the controls (right and left pooled) is shown with dashed brown line. (* $p < 0.05$ and ** $p < 0.01$ and *** $p < 0.001$ with paired two-sample [comparing the means of different time points, and the means of affected and unaffected hemispheres in patients] or two-sample t-test [comparing the means of controls and patients]).

Patients versus healthy controls

The response energy of contralateral UH was larger in patients than in controls at T1 and T2 (T1 and T2 $p < 0.001$). In the affected (AH) contralateral hemisphere, response energy was larger in patients than in controls only at T2 ($p < 0.001$.)

In the ipsilateral side with respect to the stimulated hand, the response energy was significantly larger in patients than in controls at T1 and at T2 in the AH ($p < 0.05$ for T1; $p < 0.005$ for T2) and at all time points in the UH ($p < 0.005$ for T0; $p < 0.001$ for T1; $p < 0.001$ for T2).

The p-values of the statistical analysis are shown in Appendix A.

4.2 Passive movement

4.2.1 Grand averages

The grand averages were calculated to find out when the responses to passive movement appear, what are the reasonable time windows for searching the responses with largest amplitudes and what is a suitable time window for the response energy measurement. The grand averages indicate that the responses to passive movement occurred within 1200 ms after the stimulus onset. (See Fig. 18 and 19).

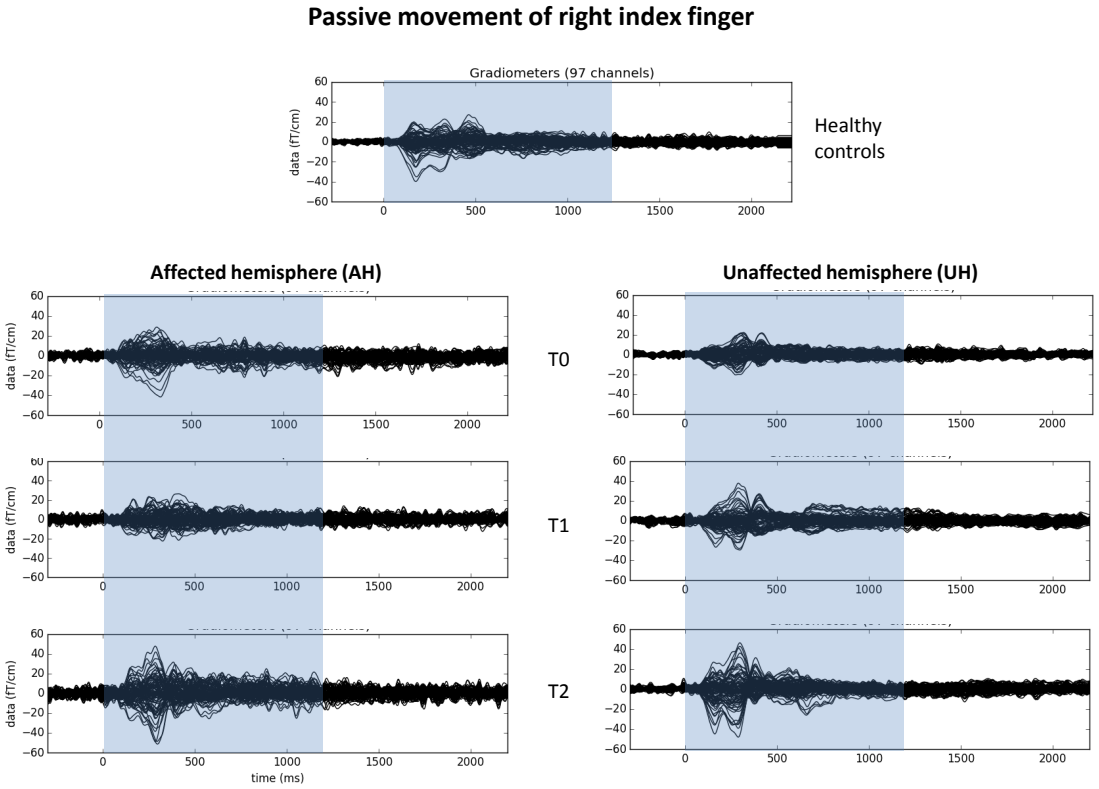

Figure 18: Superimposed grand-average responses recorded from the hemisphere contralateral to passive movement of right index finger. Most responses occur within 1200 ms after the stimulus onset.

Figure 20 and Figure 21 show grand average responses to passive movement of the right index finger and left index finger respectively. The insets show enlarged responses from two locations. Grand averages indicate that passive movement of the index finger elicited three main responses over the parietal region in the hemisphere contralateral to the stimulated hand. The first response peaked on average 150–200 ms, the second 280–320 ms and the third 390–460 ms after the movement onset. The peak latency of the strongest response on the ipsilateral side varied to a great extent. It peaked between 280 and 480 ms after the movement onset and the polarity of the response as well as the location varied highly. Thus, consistent ipsilateral responses were not found.

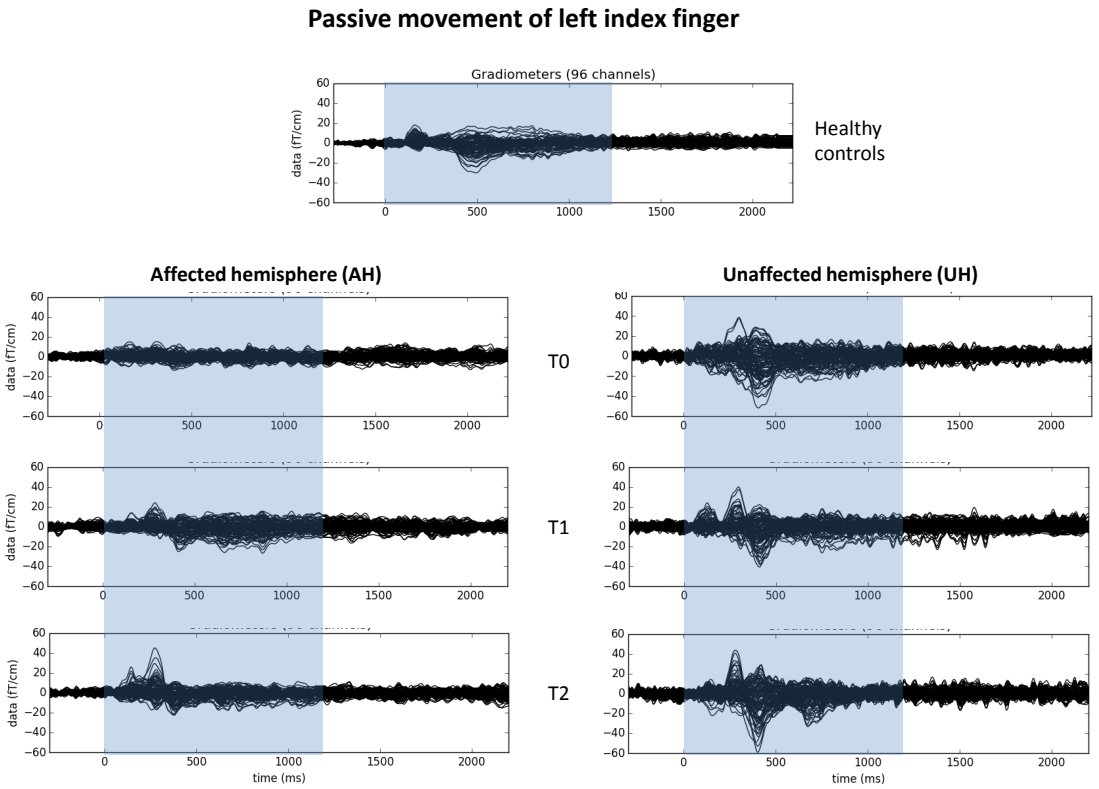

Figure 19: Superimposed grand-average responses recorded from the hemisphere contralateral to passive movement of left index finger. Most responses occur within 1200 ms after the stimulus onset.

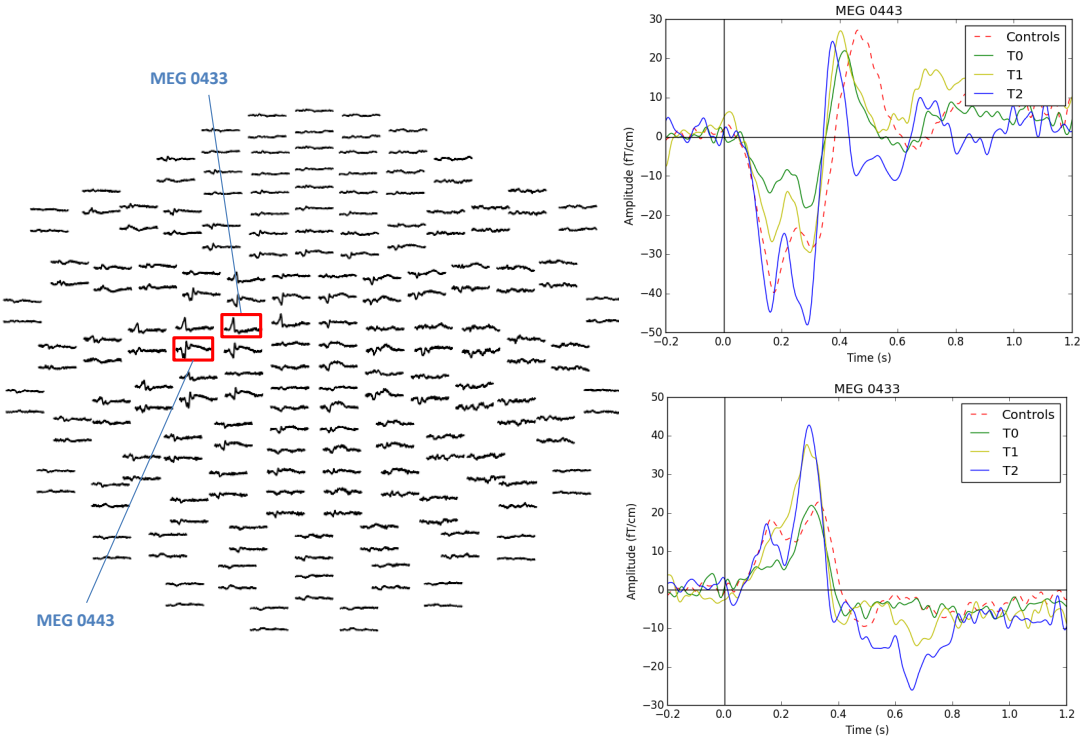

Figure 20: Distribution of the cortical responses of patients and healthy controls to passive movement of the right index finger (healthy hand). The view is from above the head with the nose pointing upwards. The largest responses occur in the frontoparietal planar channels above the contralateral left hemisphere. Enlarged responses from the encircled channels are shown on the right.

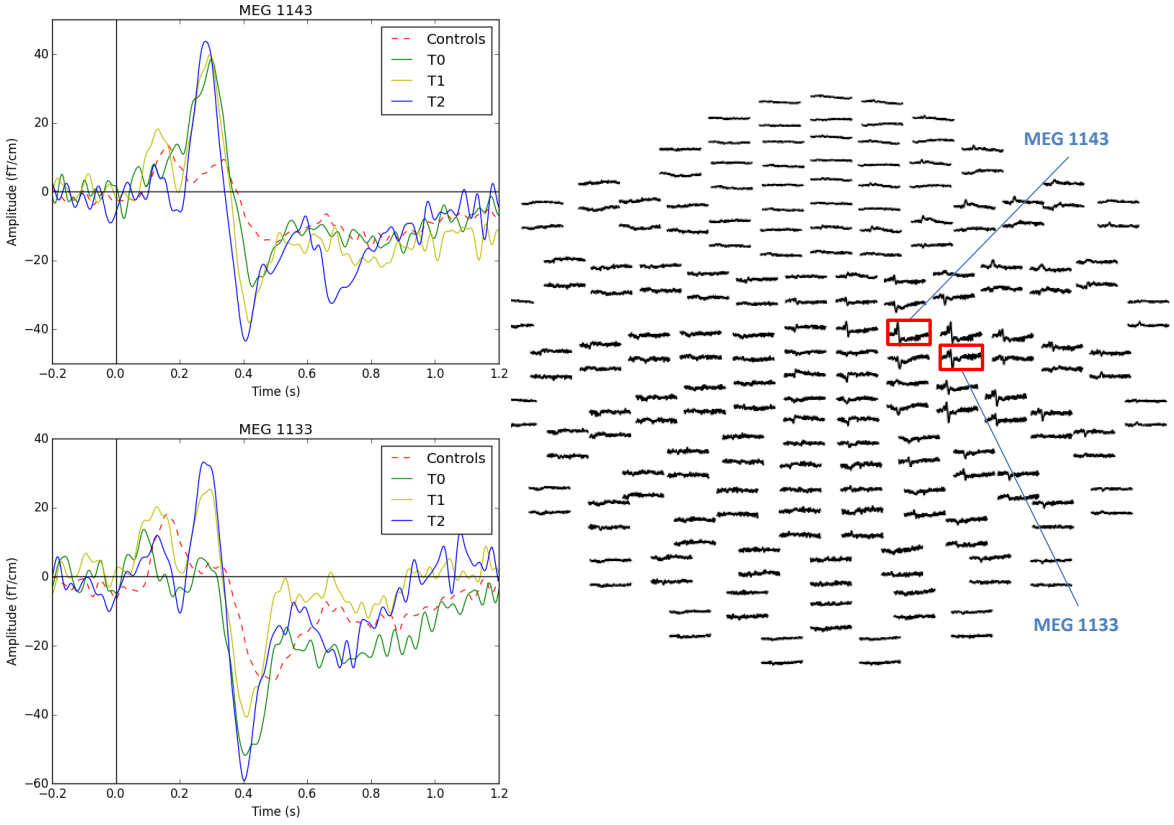

Figure 21: Distribution of the cortical responses of patients and healthy controls to passive movement of the left index finger (healthy hand). The view is from above the head with the nose pointing upwards. The largest responses occur in the frontoparietal planar channels above the contralateral right hemisphere. Enlarged responses from the encircled channels are shown on the left.

4.2.2 Response amplitudes and latencies

Passive movement of the index finger elicited three main responses in the contralateral hemisphere. The second and third responses were more distinguishable and slightly stronger than the first response and thus the first response was left out of the measurements of response amplitudes. The second response peaked at around 300 ms after the stimulus onset and is thus called evoked response PASS300 in this study. The PASS300 peak amplitudes were searched in each subject and measurement by calculating the largest amplitude of the response deflection within a time window 270–360 ms after the movement onset. The third response peaked on average at 410 ms after the stimulus onset and is called evoked response PASS410. The PASS410 peak amplitudes were searched using a time window 370–480 ms. The peak amplitudes and the corresponding latencies are shown in Table 5. The peak amplitudes on the ipsilateral side were not studied as no consistent activation could be found.

In the MEG measurement, every subject had an individual delay between the measured stimulus onset time and the real onset time. These delays were calculated for each subject separately using accelerometer signals. In subjects that were lacking accelerometer signals, the mean delay was used, which may cause the latencies to be inaccurate.

Table 5: Mean (+SEM) energies, peak latencies and corresponding amplitudes of responses to index finger extension. The response energies are measured from the both contralateral and ipsilateral side with respect to the stimulated hand. Recordings made at 1–7 days (T0), 1 month (T1), and 12 months (T2) after the stroke. UH = unaffected hemisphere in patients, AH = affected hemisphere in patients.

	2nd response		3rd response		Response energy	
	Latency (ms)	Amplitude (fT/cm)	Latency (ms)	Amplitude (fT/cm)	Contralateral (fT/cm)*s	Ipsilateral (fT/cm)*s
Controls	312 ± 7	52 ± 4	447 ± 6	54 ± 3	485 ± 22	383 ± 23
T0 UH	326 ± 4	43 ± 3	419 ± 6	51 ± 7	474 ± 41	473 ± 44
T1 UH	304 ± 6	57 ± 5	399 ± 9	56 ± 7	521 ± 41	599 ± 98
T2 UH	291 ± 6	73 ± 7	393 ± 6	74 ± 8	603 ± 46	577 ± 59
T0 AH	308 ± 6	45 ± 5	423 ± 7	39 ± 4	479 ± 56	304 ± 25
T1 AH	308 ± 7	48 ± 5	415 ± 11	63 ± 8	607 ± 67	369 ± 29
T2 AH	299 ± 7	68 ± 8	397 ± 7	67 ± 6	609 ± 48	450 ± 38

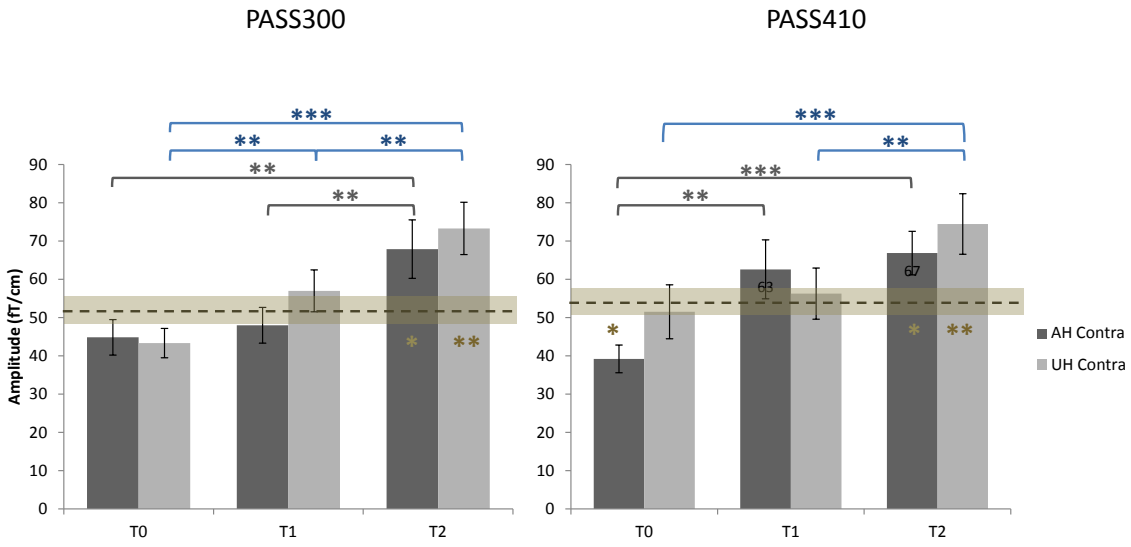

Figure 22: Mean peak amplitudes of the P300 and P410 responses of the patients to passive stimulation to the affected (AH) and unaffected (UH) hand. The mean amplitudes of the controls are shown with dashed red lines. (* $p < 0.05$ and ** $p < 0.01$ and *** $p < 0.001$ with paired two-sample [comparing the means of different time points, and the means of affected and unaffected hemispheres in patients] or two-sample t-test [comparing the means of controls and patients]).

Temporal evolution

The peak latency of the PASS300 response in the UH decreased significantly from T0 to T1 and onward to T2 (326 ms > 304 ms >291 ms, $p < 0.005$ for T1 vs. T0, $p < 0.05$ for T2 vs. T1, $p < 0.001$ for T2 vs. T0). Similarly, the peak latency of the PASS410 response in the both AH and UH peaked significantly earlier at T2 than at T0 (397 ms < 423 ms, $p < 0.005$ for AH and 393 ms < 419 ms, $p < 0.005$ for UH).

The amplitudes of the both P300 and P410 responses increased significantly from T0 to T2 in both the AH and UH as shown in Fig. 22 ($p < 0.01$ for P300 (AH) and for P410 (UH); $p < 0.001$ for P300 (UH) and for P410 (AH)). In addition, both responses increased significantly from the T1 to T2 in the UH ($p < 0.01$ for P300).

Affected versus unaffected hemisphere

The PASS300 response peaked significantly earlier in the AH than in the UH at T0 (308 ms vs. 326 ms, $p < 0.05$). No significant differences detected in the peak amplitudes between the hemispheres.

Patients versus healthy controls

The PASS410 response in the AH and UH peaked significantly earlier in patients than controls at all time points ($p < 0.05$ for AH, $p < 0.001$ for UH) but this may be due to the inaccurate latencies.

Moreover, the peak amplitudes P300 and P410 were significantly stronger in patients than in control subjects at T2 in the both AH and UH ($p < 0.05$ for P300 and P410 (AH); $p < 0.005$ for P300 (UH); $p < 0.01$ for P410 (UH)). In contrast, the P410 response was smaller in patients than in controls at T0 in AH ($p < 0.005$).

The mean ($\pm$ SEM) peak amplitudes of passive movement and corresponding p-values of the statistical analysis are shown in Appendix B.

4.2.3 Response energy

The response energy was calculated to measure the total activity in the somatosensory cortices of one hemisphere elicited by the passive movement of the index finger. The grand averages showed that the responses to passive movement occurred within 1200 ms after the movement onset. Therefore, the suitable time window for the response energy measurement was 0–1200 ms (see Fig. 18). The results of the response energy measurement are shown in Table 5.

Temporal evolution

The response energy evoked to passive moment of the index finger was growing from the first measurement (T0) to the last measurement (T2) as shown in Fig. 23. The response energy was significantly larger at T2 than at T0 on both the contralateral ($p < 0.01$ for AH; $p < 0.05$ for UH) and ipsilateral ($p < 0.001$ for AH; $p < 0.01$ for UH) affected and unaffected hemispheres. In addition, the energy increased significantly from T0 to T1 in the AH and from T1 to T2 in the UH ($p < 0.05$).

Affected versus unaffected hemisphere

The response energy was significantly smaller in the AH than UH at all time points on the ipsilateral side with respect to the stimulated hand ($p < 0.001$ for T0; $p < 0.01$ for T1; $p < 0.05$ for T2). However, this phenomenon was not detected on the contralateral hemisphere.

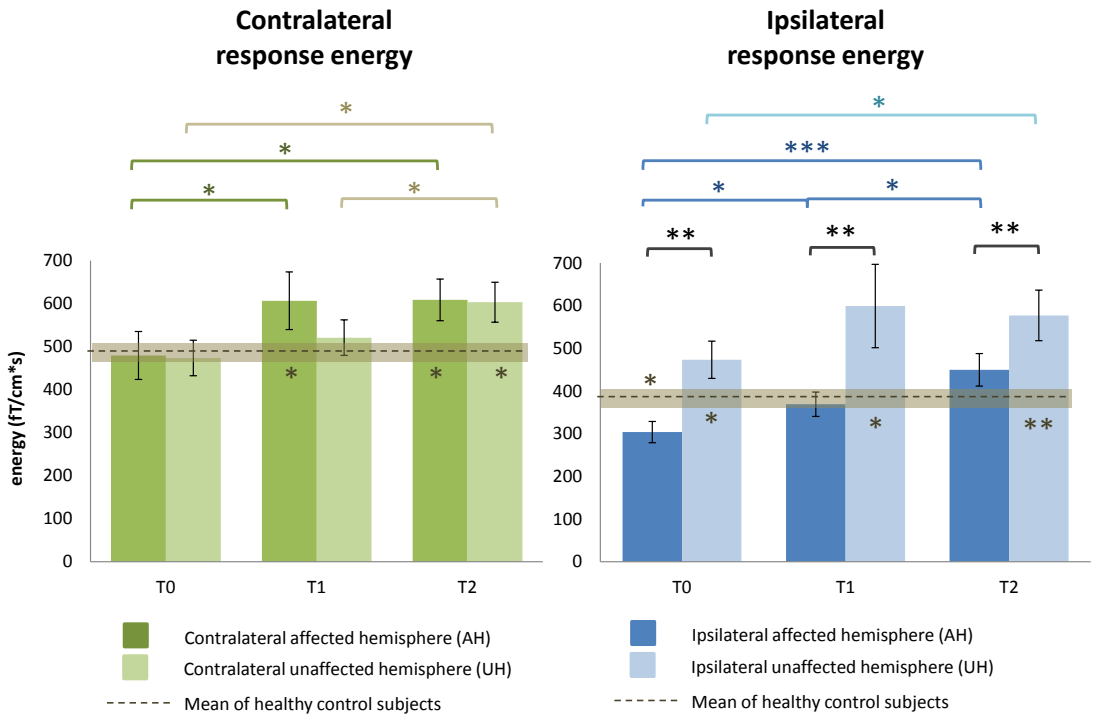

Figure 23: Mean (± SEM) energy of contralateral and ipsilateral responses to passive movement of index finger of the patients. The mean response energy of the controls (right and left hemispheres pooled) are shown with dashed brown line. (* $p < 0.05$ and ** $p < 0.01$ and *** $p < 0.001$ with paired two-sample [comparing the means of different time points, and the means of affected and unaffected hemispheres in patients] or two-sample t-test [comparing the means of controls and patients]).

Patients versus healthy controls

The patients had a significantly larger response energy than the control subjects at T2 in the both contralateral AH and UH ($p < 0.05$). In addition, the energy was significantly larger in patients than in controls at all time points on the ipsilateral side with respect to the healthy hand stimulation ($p < 0.05$ for T0 and for T1; $p < 0.005$ for T2). However, the energy was significantly smaller in patients than in controls at T0 on the ipsilateral side with respect to the impaired hand stimulation ($p < 0.05$).

The p-values of the statistical analysis are shown in Appendix B.

5 Discussion

The aim of the thesis was to examine how activity in somatosensory cortex changes during stroke recovery. The MEG measurements were made at the acute phase at 1-7 days (T0), at one month (T1) and at 12 months (T2) after stroke onset. Tactile stimulus to the index finger elicited two main responses in the contralateral hemisphere with respect to the stimulated hand. The first one peaked on average at 60 ms (TACT60) and the second on average at 100 ms (TACT100) after the stimulus onset, in line with previous studies (Forss et al., 1994b, 1999; Simões et al., 2001; Druschky et al., 2003b; Karageorgiou et al., 2008). Even though the source modeling was not carried out, we speculate the TACT60 response is related to the response in the SI and the TACT100 response is related to the SII.

Passive movement of the index finger elicited three main responses in the contralateral hemisphere with respect to the stimulated hand. The responses peaked between 150 ms and 460 ms after the passive movement onset; the two strongest peaked on average at 300 ms (PASS300) and at 410 ms (PASS410). Most of the previous studies have detected responses within 0–300 ms after the passive movement onset and are focused on examining the first visible responses. Moreover, Druschky and colleagues (2003b) have identified contralateral SEF components at cortical regions outside SI at 150–500 ms after passive movement. However, the results are difficult to compare due to the different measurement methods. The previous studies have used custom-built mechanical devices (except Onishi et al. (2013)) to lift the index finger, unlike in the data used in this study, where the finger was lifted manually by an assisting person. Because of the manual method, the time delay varies between subjects and duration of the movement, range of the finger extension and angular velocity are not constant. Moreover, Sugawara and colleagues (2016) have shown that some responses to passive movement are dependent on duration of the movement or angular velocity. Besides, the previous studies have used ISIs up to 10 s whereas this study used an ISI of 3 s.

The analysis in this work did not only deal with the individual peak amplitudes, but also a response energy was calculated to detect the entire activity elicited by the tactile or passive stimulus. The response energy sums up the total activity from different sources of the somatosensory areas of one hemisphere. No such studies of response energy following tactile stimulation or passive movement have been previously reported. Moreover, to our knowledge, this is the first follow-up study to research somatosensory evoked responses to passive movement in several stroke patients.

Finally, the results of the passive movement were similar to the results of the tactile stimulus for the three research questions. Due to this similarity, the results will be discussed together.

Temporal profile of the activity

One of the research aims was to clarify the temporal profile of recovery by comparing the strength of somatosensory cortex activation at the acute phase, one month and

12 months after the stroke symptoms. The results of the TACT100 response and response energy of tactile stimulus indicate that the somatosensory cortex activation was significantly stronger at 12 months (T2) than at 1–7 days (T0) after the stroke in both the contralateral affected and unaffected hemispheres with regard to the stimulated hand. The results are in line with previous studies; for example, Forss and colleagues (2012) noticed that the contralateral response in the second somatosensory cortex (SII) around 109 ms to the tactile stimulus was significantly weaker at acute phase than at one and three months post-stroke. In addition, the results of this study showed that the somatosensory cortex activation in the affected hemisphere was growing significantly from one month (T1) to 12 months (T2) post-stroke, whereas the follow-up period ended at 3 months in the study of Forss and colleagues (2012).

Similarly, the somatosensory activity elicited by passive movement of the index finger increased during the follow-up. The response energy and peak amplitudes to passive movement of the index finger significantly increased from 1–7 days (T0) to 12 months (T2) post-stroke in both affected and unaffected hemispheres. In addition, the results indicate that with respect to the affected hand stimulation, the growth was significant from the acute phase (T0) to one month (T1) post-stroke, and with respect to the healthy hand stimulation, the growth was significant from one month (T1) to 12 months (T2) post-stroke in the contralateral hemisphere. The results are in line with those of Druschky and colleagues (2003a), who detected that the contralateral SEF amplitude in the affected hemisphere increased from two weeks to six months after the infarct. However, Druschky and colleagues (2003a) studied only one male patient with ischemic stroke in the right median cerebral artery territory while we studied 23 patients of both genders. The results are also in line with those of Parkkonen and colleagues (2017) who studied the same data; however, they studied 20-Hz motor-cortex instead of evoked responses. Similarly, they observed that the rebound was increased significantly from the acute phase to 12 months post-stroke in both the affected and unaffected hemispheres and also from the acute phase to 1 month post-stroke in the affected hemisphere. No other earlier studies of the passive movement of stroke patients have been reported.

Both, the response energy and peak amplitudes of responses elicited to tactile stimulus and passive movement of index finger indicate that the somatosensory responses are strengthened over time in stroke patients which is in line with earlier studies (Huang et al., 2004; Forss et al., 2012; Druschky et al., 2003a). The reduced activation in the affected hemisphere at acute phase may be due to injured afferent inputs or direct damage to somatosensory processing areas in the brain. The significantly increasing responses during recovery are probably caused by resolution of edema and reperfusion of the ischemic penumbra at an early phase and later on by unmasking of latent connections and reorganization of functional architecture and connections of somatosensory brain areas, elicited by changes of excitability. The finding that somatosensory responses grow significantly in the unaffected hemisphere implies that changes of excitability occur also in the healthy hemisphere. On the other hand, long latency responses are known to be very sensitive to attention and vigilance, and as the acute stroke patients tend to be somnolent in the acute phase, this may have had a substantial effect on the results. Moreover, SI responses are

less vulnerable to vigilance changes, and no significant increase in response strength between T0 and T1 or between T0 and T2 was observed in TACT60 responses (see Fig. 16), suggesting that changes in vigilance might explain partly the changes in response strengths. The results of this work indicate that neurological changes occur for 12 months after the stroke. In the future, studies of the passive-movement responses between 3 months and 12 months post-stroke would give more knowledge about the temporal evolution of the responses on the late phase of the recovery.

Furthermore, this study indicates that the response energy increased significantly also in the ipsilateral affected hemisphere with regard to the tactile stimulus or passive movement of the index finger during the follow-up. The results suggest that also these ipsilateral brain areas are affected by stroke. However, only the energy, but not peak amplitudes, of the ipsilateral responses were analysed in this study.

Comparing the activity between affected and unaffected hemispheres

When the somatosensory evoked responses are compared between the affected and unaffected hemispheres, the results indicate that the activity elicited by the tactile stimulus is stronger in the unaffected hemisphere than in the affected hemisphere at one month after the stroke (T1). The results are in line with earlier studies (Roiha et al., 2011; Forss et al., 2012) however, they detected significant differences between the hemispheres also in the acute phase (T0), which was not observed in this study. The magnitude of the responses between hemispheres did not differ in healthy control subjects. The different results between patients and healthy subjects are likely due to the changes in excitatory–inhibitory circuits. Normally, both hemispheres inhibit each other; when one hemisphere is damaged, the inhibition of the healthy hemisphere decreases and thus, the activity of the healthy hemisphere strengthens (Forss et al., 1999). In healthy subjects, the inhibition feedback is kept, therefore accounting for the observed difference.

In contrast to tactile stimulus, no significant differences in contralateral responses with respect to the stimulated hand between the hemispheres were observed after the passive movement. On the other hand, the results of both tactile and passive stimulations indicate that the response energy on the ipsilateral side with respect to the stimulated hand is larger in the unaffected hemisphere than in the affected hemisphere at all time points. As shown in the Fig. 17 and 23, the results imply that the activity in the ipsilateral healthy hemisphere is enhanced when impaired hand is stimulated, which explains why the activity is stronger in the unaffected than affected ipsilateral hemisphere at all time points. The ipsilateral somatosensory cortex is assumed to be activated by direct thalamic connections (Forss et al., 1999; Schrafl-Altermatt et al., 2014) rather than through transcallosal connections and thus, are not necessarily dependent on activation of the contralateral somatosensory cortex. Moreover, based on studies of monkeys e.g. (Burton, 1986), part of neurons inside the SII region responds only to the contralateral stimulation whereas others respond only to the ipsilateral stimulations and a large part respond to both ipsilateral and contralateral stimulations. Thus, a different populations of neurons in one hemisphere responds to contralateral stimulus than to ipsilateral stimulus. These are rational

reasons to explain the differences between the results of contralateral and ipsilateral hemispheres.

Comparing the activity between patients and healthy control subjects

The third research question concerns the relationship of the somatosensory evoked responses between stroke patients and healthy control subjects. The results establish that the somatosensory evoked responses to the tactile stimulus and passive movement of the index finger are significantly stronger in patients than control subjects at 12 months after the infarct. This phenomenon was observed in both affected and unaffected hemispheres. On the other hand, the tactile response TACT100 and the passive response PASS410 and energy in the affected hemisphere were weaker in the patients than in controls at acute phase.

In addition, the response energy on the unaffected ipsilateral hemisphere, with respect to the stimulated hand (both tactile and passive), was significantly stronger in patients than control subjects at all time points. This is due to the enhanced activity in the ipsilateral unaffected hemisphere elicited by the impaired hand stimulation which was discussed earlier. The enhanced activity of ipsilateral unaffected hemisphere is probably due to the damaged SII in the affected hemisphere. The damaged SII or its damaged connections may result to unmasking the pre-existing silent, normally inhibited, ipsilateral connections to strengthen.

Enhanced activation of the healthy hemisphere may have an effect to abnormally inhibit the lesioned hemisphere, which may cause incomplete recovery (Forss et al., 1999; Manganotti et al., 2002; Ward et al., 2003). The impaired hand function of the patients in the present study did not reach the level of the healthy hand by 12 months, which may explain the enlarged responses in the healthy hemisphere. After a stroke, the inhibition of both hemispheres decreases so that formation of new synapses and re-wiring can occur. This means that the activity in the cortex increases. Further, earlier studies have shown that normalization of the inhibitory level decreased the brain activity and, is a prerequisite for good recovery of the hand function (Laaksonen et al., 2012). During re-learning of motor skills, more resources are required from the brain, whereby the hand representation area and the evoked responses in the brain increase, whereas, the normalization of the representation size and the reduced responses could be seen as a sign of maintenance of re-learned function (Roiha et al., 2011). Since the activity is significantly growing and is stronger in patients than controls at 12 months post-stroke, implies that the hemispheres are lacking proper inhibition which in turn is related to poor recovery. However, it might be related also to the site of the lesion. Luft and colleagues (2004) detected that overall brain activation was lower in patients with cortical stroke than in healthy controls, while the activation was larger in subcortical patients than control subjects. In the present study, six patients had a subcortical, 15 had a cortico–subcortical, and only two had a mere cortical lesion. Therefore in almost all of the patients had a subcortical or cortico–subcortical lesion, which might explain why the mean activity of all patients is stronger than the mean activity of control subject.

Limitations of the study

The individual peak amplitudes of the responses from patients were not always easy to distinguish especially from the affected hemisphere and at acute phase (T0) after the stroke. Because the passive movements were performed manually, the latencies of the responses varied slightly between subjects. This made the detecting and comparing of the passive responses even more difficult. In future studies, repeatability of the passive movement is suggested to perform by a mechanical device, instead of lifting the finger manually, to obtain more accurate results. In addition, source modeling could not be performed in this study, so even though, the responses likely refer to the same sources it is not certain that all the compared peak amplitudes are from the same sources.

Further, ipsilateral peak amplitudes with respect to the stimulated hand were not studied as no consistent activation could be found. The ipsilateral activity was studied only by measuring the whole generated activity in the selected channels by mean of the energy response.

A correlation between the somatosensory activity and clinical outcomes was not carried out in this study due to limited time, but it could give important information about the relationship between the somatosensory activity and functional recovery.

6 Conclusions

The aim of the thesis was to examine how activity in somatosensory cortex changes during stroke recovery. The main goals were to study whether this activity grows during recovery, and compare it between affected and unaffected hemispheres as well as between patients and healthy control subjects. The results confirmed that a stroke changes both proprioceptive and tactile information processing and a unilateral stroke affects both damaged and healthy hemispheres. Moreover, the results indicate that the activity changes during one-year follow-up, which refers that neural changes occur within first three months but can continue significantly up to 12 months.

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A *p*-values of the statistical analysis (tactile stimulus)

The upper part of the tables show the mean (± SEM) SEF energies and mean (± SEM) peak amplitudes (TACT60 and TACT100) of somatosensory evoked fields in patients and in healthy controls to tactile stimulus of index finger. AH = affected hemisphere, UH = unaffected hemisphere. Lower part of the tables show *p*-values of the t-test (paired two-sample and two-sample t-tests). Growth = comparison between acute phase (T0) and one month post-stroke (T1) and 12 months post-stroke (T2). AH vs. UH = Comparison between affected and unaffected hemispheres. Pts vs. Ctrls = comparison between patients and control subjects. The green color indicates that the *p*-value is under 0.05, and the gray color that the *p*-value is equal to or under 0.07.

	Response energy (fT/cm)*s		
	T0	*T1*	*T2*
AH contra	235 ± 26	236 ± 16	275 ± 22
UH contra	250± 19	268 ± 13	297 ± 22
Ctrls contra	214 ± 10		
AH ipsi	143 ± 11	158 ± 10	173 ± 12
UH ipsi	215 ± 26	225 ± 25	228 ± 21
Ctrls ipsi	134 ± 6		

	p -values		
Growth	*T0 vs. T1*	*T1 vs. T2*	*T0 vs. T2*
AH contra	0.4721	0.0051	0.0435
UH contra	0.1118	0.0859	0.0180
AH ipsi	0.0222	0.1078	0.0174
UH ipsi	0.3586	0.4189	0.3025
AH vs. UH	***T0***	***T1***	***T2***
Contra	0.2783	0.0329	0.0704
Ipsi	0.0021	0.0029	0.0027
Pts vs. Ctrls	***T0***	***T1***	***T2***
AH contra	0.2365	0.1351	0.0069
UH contra	0.0529	0.0008	0.0007
AH ipsi	0.2456	0.0223	0.0038
UH ipsi	0.0024	0.0007	0.0001

	Peak amplitudes (fT/cm)		
	T0	*T1*	*T2*
AH TACT60	71 ± 9	68 ± 8	82 ± 9
UH TACT60	78 ± 7	86 ± 7	96 ± 9
Ctrls TACT60	63 ± 3		
AH TACT100	55 ± 5	66 ± 6	88 ± 8
UH TACT100	88 ± 10	98 ± 7	114 ± 11
Ctrls T100	88 ± 6		

	p -values		
Growth	*T0 vs. T1*	*T1 vs. T2*	*T0 vs. T2*
AH TACT60	0.3445	0.0207	0.0655
UH TACT60	0.1522	0.1358	0.0628
AH TACT100	0.0151	0.0018	0.0003
UH TACT100	0.1198	0.0272	0.0139
AH vs UH	***T0***	***T1***	***T2***
TACT60	0.1736	0.0267	0.1296
TACT100	0.0004	0.0008	0.0122
Pts vs. Ctrls	***T0***	***T1***	***T2***
AH TACT60	0.2119	0.2819	0.0329
UH TACT60	0.0346	0.0043	0.0015
AH TACT100	0.0001	0.0088	0.4749
UH TACT100	0.4823	0.1453	0.0215

	Peak latencies (ms)		
	T0	*T1*	*T2*
AH TACT60	64 ± 1.8	66 ± 2.1	59 ± 1.3
UH TACT60	61 ± 1.3	61 ± 1.1	60 ± 1.2
Ctrls TACT60	63 ± 1.0		
AH TACT100	107 ± 3.3	101 ± 2.7	101 ± 2.9
UH TACT100	100 ± 2.6	99 ± 2.0	99 ± 2.8
Ctrls T100	101 ± 2.1		

	p -values		
Growth	*T0 vs. T1*	*T1 vs. T2*	*T0 vs. T2*
AH TACT60	0.2906	0.0058	0.0002
UH TACT60	0.2908	0.4817	0.3495
AH TACT100	0.1219	0.4615	0.0575
UH TACT100	0.2064	0.3377	0.3816
AH vs UH	***T0***	***T1***	***T2***
TACT60	0.0963	0.0191	0.2595
TACT100	0.0646	0.2171	0.3431
Pts vs. Ctrls	***T0***	***T1***	***T2***
AH TACT60	0.2577	0.1174	0.0140
UH TACT60	0.1172	0.0556	0.0684
AH TACT100	0.0909	0.4581	0.4215
UH TACT100	0.3681	0.1663	0.2838

B *p*-values of the statistical analysis (passive movement)

The upper part of the tables show the mean (± SEM) energies and mean (± SEM) peak amplitudes (PASS300 and PASS410) of somatosensory evoked fields in patients and in healthy controls to passive movement of index finger. AH = affected hemisphere, UH = unaffected hemisphere. Lower parts of the table show *p*-values of the t-test (paired two-sample and two-sample t-tests). Growth = comparison between acute phase (T0) and one month post-stroke (T1) and 12 months post-stroke (T2). AH vs. UH = Comparison between affected and unaffected hemispheres. Pts vs. Ctrls = comparison between patients and control subjects. The green color indicates that *p*-value is under 0.05, and the gray color that the *p*-value is equal to or under 0.07.

	Response energy (fT/cm)*s		
	T0	*T1*	*T2*
AH contra	479 ± 56	607 ± 67	609 ± 48
UH contra	474 ± 41	521 ± 41	603 ± 46
Ctrls contra	485 ± 22		
AH ipsi	304 ± 25	369 ± 29	450 ± 38
UH ipsi	473 ± 44	599 ± 98	577 ± 59
Ctrls ipsi	383 ± 23		

	p-values		
Growth	*T0 vs. T1*	*T1 vs. T2*	*T0 vs. T2*
AH contra	0.0286	0.4756	0.0039
UH contra	0.1276	0.0130	0.0108
AH ipsi	0.0229	0.0285	0.0001
UH ipsi	0.0567	0.3483	0.0096
AH vs. UH	*T0*	*T1*	*T2*
Contra	0.4662	0.0489	0.4559
Ipsi	0.0003	0.0093	0.0150
Pts vs. Ctrls	*T0*	*T1*	*T2*
AH contra	0.4649	0.0479	0.0151
UH contra	0.4063	0.2230	0.0141
AH ipsi	0.0111	0.3513	0.0700
UH ipsi	0.0378	0.0209	0.0025

	Peak amplitudes (fT/cm)		
	T0	*T1*	*T2*
AH PASS300	45 ± 5	48 ± 5	68 ± 8
UH PASS300	43 ± 3	57 ± 5	73 ± 7
Ctrls PASS300	52 ± 4		
AH PASS410	39 ± 4	63 ± 8	67 ± 6
UH PASS410	51 ± 7	56 ± 7	74 ± 8
Ctrls PASS410	54 ± 3		

	p-values		
Growth	*T0 vs. T1*	*T1 vs. T2*	*T0 vs. T2*
AH PASS300	0.2893	0.0070	0.0027
UH PASS300	0.0064	0.0009	0.0002
AH PASS410	0.0027	0.2400	0.0001
UH PASS410	0.2138	0.0063	0.0049
AH vs. UH	*T0*	*T1*	*T2*
PASS300	0.3953	0.0727	0.3153
PASS410	0.0793	0.2415	0.1694
Pts vs. Ctrls	*T0*	*T1*	*T2*
AH PASS300	0.1183	0.2568	0.0335
UH PASS300	0.0548	0.2197	0.0026
AH PASS410	0.0021	0.1542	0.0286
UH PASS410	0.3793	0.3774	0.0078

	Peak latencies (ms)		
	T0	*T1*	*T2*
AH PASS300	308 ± 6	308 ± 7	299 ± 7
UH PASS300	326 ± 4	304 ± 6	291 ± 6
Ctrls PASS300	312 ± 7		
AH PASS410	423 ± 7	415 ± 11	397 ± 7
UH PASS410	419 ± 6	399 ± 9	393 ± 6
Ctrls PASS410	447 ± 6		

	p-values		
Growth	*T0 vs. T1*	*T1 vs. T2*	*T0 vs. T2*
AH PASS300	0.4964	0.1332	0.0893
UH PASS300	0.0019	0.0312	0.0000
AH PASS410	0.2424	0.0672	0.0043
UH PASS410	0.0296	0.2700	0.0020
AH vs. UH	*T0*	*T1*	*T2*
PASS300	0.0134	0.3353	0.2293
PASS410	0.3020	0.1681	0.3361
Pts vs. Ctrls	*T0*	*T1*	*T2*
AH PASS300	0.3245	0.3318	0.0899
UH PASS300	0.0515	0.1955	0.0193
AH PASS410	0.0063	0.0081	0.0000
UH PASS410	0.0010	0.0001	0.0000